



Clinical trial results:

A phase Ib study of metronomic Cyclophosphamide and Methotrexate combined with Zoledronic acid and Sirolimus in patients with solid tumor with bone metastasis and advanced pretreated Osteosarcoma.

Summary

EudraCT number	2014-000196-85
Trial protocol	FR
Global end of trial date	16 November 2021

Results information

Result version number	v1 (current)
This version publication date	03 January 2024
First version publication date	03 January 2024

Trial information

Trial identification

Sponsor protocol code	IB_2014-01
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut Bergonié
Sponsor organisation address	229 cours de l'Argonne, Bordeaux, France, 33076
Public contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr
Scientific contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr

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	08 March 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the recommended phase II dose, the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D28), the safety profile, and the Dose Limiting Toxicities (DLT) of sirolimus when prescribed in combination with Metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA) in patients with solid tumor with bone metastasis and advanced pretreated osteosarcoma.

Protection of trial subjects:

The study was supervised and monitored by a Steering Committee. This committee ensured the following:

- Implementation and regular follow-up of the study
- Patient protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

An independent Data Monitoring Committee (IDMC) was created at the request of the relevant Authority, the sponsor or the Steering Committee. The IDMC plays an advisory role for the Sponsor, who has the final decision regarding the implementation of recommendations put forward by the IDMC. This Committee must comprise at least one qualified oncologist, one pharmacologist and one statistician.

The IDMC is responsible for the following:

- Analyzing preliminary efficacy and safety data,
- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of efficacy) or publication of the trial results,
- Drafting the minutes after each meeting and monitoring their confidentiality.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2015
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	France: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	1
Adults (18-64 years)	15
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Upon signature of consent, eligible patient were entered in the study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator.

Pre-assignment

Screening details:

Upon signature of consent, the Coordinator will assign a patient screening number.

Upon results of pathological review will be available, the CRA at Institut Bergonie should inform site by e-mail and return results by fax.

Period 1

Period 1 title	All study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	4 mg Sirolimus
Arm description: -	
Arm type	First dose level
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cycle Length=28 days

- Twice a day 50mg b.i.d.
- In the morning and evening
- One week on / one week off

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

Dosage and administration details:

Cycle Length=28 days

- Twice a day 2.5mg b.i.d.
- In the morning and evening
- On day 1 and day 4, every week

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

Dosage and administration details:

Cycle length=28 days

Administration on day 2 of each cycle

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Cycle Length= 28 days	
- 4 mg once a day	
- In the morning	
Arm title	6mg Sirolimus
Arm description: -	
Arm type	Second dose level
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Cycle Length=28 days	
- Twice a day 50mg b.i.d.	
- In the morning and evening	
- One week on / one week off	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Cycle Length=28 days	
- Twice a day 2.5mg b.i.d.	
- In the morning and evening	
- On day 1 and day 4, every week	
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Cycle length=28 days	
Administration on day 2 of each cycle	
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Cycle Length= 28 days	
- 6 mg once a day	
- In the morning	
Arm title	Expansion cohort
Arm description: -	
Arm type	single-arm
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cycle Length=28 days

- Twice a day 50mg b.i.d.
- In the morning and evening
- One week on / one week off

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

Dosage and administration details:

Cycle Length=28 days

- Twice a day 2.5mg b.i.d.
- In the morning and evening
- On day 1 and day 4, every week

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

Dosage and administration details:

Cycle length=28 days

Administration on day 2 of each cycle

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cycle Length= 28 days

- 4 mg once a day
- In the morning

Number of subjects in period 1	4 mg Sirolimus	6mg Sirolimus	Expansion cohort
Started	6	3	14
Completed	6	3	14

Baseline characteristics

Reporting groups

Reporting group title	All study
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Reporting group description: -

Reporting group values	All study	Total	
Number of subjects	23	23	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	40.8		
inter-quartile range (Q1-Q3)	26 to 79.5	-	
Gender categorical			
Units: Subjects			
Female	12	12	
Male	11	11	

End points

End points reporting groups

Reporting group title	4 mg Sirolimus
Reporting group description: -	
Reporting group title	6mg Sirolimus
Reporting group description: -	
Reporting group title	Expansion cohort
Reporting group description: -	

Primary: Dose limiting toxicity (DLT)

End point title	Dose limiting toxicity (DLT) ^{[1][2]}
End point description: Adverse event (AE) or laboratory abnormality that fulfills the criteria below: <ul style="list-style-type: none">- Is considered to be at least possibly related to the study treatment- Is unrelated to disease, disease progression, inter-current illness, or concomitant medications- Meets one of the criteria below, graded as outlined or according to NCI CTCAEv4.3:<ul style="list-style-type: none">o Grade 4 non-haematological toxicity (not laboratory) or lymphopeniao Grade 3 non-haematological toxicity > 3 days (not laboratory) (except for asthenia, 1st episode of nausea/vomiting without maximal symptomatic/prophylactic treatment)o Grade ≥ 3 non-hematologic laboratory value if medical intervention is required to treat the patient, or the abnormality leads to hospitalization, or the abnormality persists for > 1 weeko Grade ≥ 3 hematologic toxicity > 3 dayso Confirmed febrile neutropenia- In addition treatment temporary interruption or dose modification leading to dose intensity lower than 70% are considered as DLT 3+3 design.	
End point type	Primary
End point timeframe: First cycle of treatment	

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: DLT were assessed in the escalation part according to the traditional 3+3 design. No statistical analysis planned.

[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: DLT was primary endpoint only for dose escalation part.

End point values	4 mg Sirolimus	6mg Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: patients with at least one DLT	0	2		

Statistical analyses

No statistical analyses for this end point

Primary: 6-month non-progression

End point title	6-month non-progression ^[3] ^[4]
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End point description:

6-month non-progression rate, defined as the rate of complete (CR) or partial response (PR) or stable disease (SD) at 6 months using RECIST v1.1.

As per RECIST v1.1, progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, or a measurable increase in a non-target lesion, or the appearance of one or more new lesions.

The expansion cohort is designed to enable to detect antitumor activity observed with sirolimus combined with CP, MT and ZA.

- Sample size is calculated based on the first stage of a 2-stage Gehan design assuming a 20% efficacy rate, 5% false positive rate and 10% precision (Gehan 1961).
- 14 eligible and assessable subjects are required.
- If at least one objective response or stable disease (> 24 weeks) is observed in the 14 patients recruited in the expansion cohort, the study drug association will be considered worthy of further testing in this indication.

End point type	Primary
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End point timeframe:

Tumor assessment at 6 months using RECIST v1.1.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint in the expansion cohort was based on the first stage of a 2-stage Gehan design assuming a 20% efficacy rate, 5% false positive rate and 10% precision (Gehan 1961). No statistical analysis planned.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: 6-month non progression was primary endpoint only for expansion cohort.

End point values	Expansion cohort			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: patients with CR or PR or SD	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

OS is defined as the time from first infusion to death (of any cause)

End point values	4 mg Sirolimus	6mg Sirolimus	Expansion cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	14	
Units: Months				
median (confidence interval 95%)	12 (5.2 to 9999999)	6.6 (5.2 to 8.7)	12.8 (2.8 to 21.3)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety profile was continuously followed during treatment up to 30 days after the last treatment administration or until the start of a new antitumor therapy, whichever occurs first. All AEs will be classified according to the NCI-CTCAE, version 4.0.

Adverse event reporting additional description:

Adverse event (AE) are reported for all patients who received at least one administration of treatment. All AE and SAE (related and unrelated to treatment) are reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.3
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Reporting groups

Reporting group title	Dose escalation part – Sirolimus dose 4 mg
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Reporting group description: -

Reporting group title	Dose escalation part – Sirolimus dose 6 mg
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Reporting group description: -

Reporting group title	Expansion cohort
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Reporting group description: -

Serious adverse events	Dose escalation part – Sirolimus dose 4 mg	Dose escalation part – Sirolimus dose 6 mg	Expansion cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	2 / 3 (66.67%)	9 / 14 (64.29%)
number of deaths (all causes)	5	3	12
number of deaths resulting from adverse events	0	0	2
Investigations			
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphopenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
General physical health deterioration	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
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			
Interstitial lung disease	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (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			
Diverticulitis	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used:			

MedDRA 22.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
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			
Hypokalaemia	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia	Additional description: Occurrences causally related to treatment number included relation to the treatment according to investigator and/or sponsor.		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dose escalation part – Sirolimus dose 4 mg	Dose escalation part – Sirolimus dose 6 mg	Expansion cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 3 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subcutaneous nodule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
tumor pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Face oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	3 / 3 (100.00%)	6 / 14 (42.86%)
occurrences (all)	3	3	6
Fever			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	4 / 14 (28.57%)
occurrences (all)	1	0	4
Flu like symptoms			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
WORSENING OF GENERAL STATUS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
INFLAMMATORY SYNDROM			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
HOT FLUSHES			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
POLYDYPسيا			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Vaginal ulceration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	3 / 14 (21.43%)
occurrences (all)	3	0	3
Dyspnoea			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	3 / 14 (21.43%)
occurrences (all)	0	0	3
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
hoarseness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pleuritic pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sinus disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	5 / 14 (35.71%)
occurrences (all)	2	1	5
Alkalosis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	3 / 14 (21.43%)
occurrences (all)	1	1	3
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	2 / 3 (66.67%)	4 / 14 (28.57%)
occurrences (all)	3	2	4
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Creatine urine increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
cholesterol high			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
LDH increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
CRP increase			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lymphocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	6 / 14 (42.86%)
occurrences (all)	2	1	6
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 3 (100.00%)	2 / 14 (14.29%)
occurrences (all)	0	3	2
Platelet count decreased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 3 (100.00%)	7 / 14 (50.00%)
occurrences (all)	2	3	8
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
dysesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
paresthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 3 (66.67%)	4 / 14 (28.57%)
occurrences (all)	1	2	6
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	5 / 14 (35.71%)
occurrences (all)	2	0	5
Dry mouth			

subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Mucositis management			
subjects affected / exposed	3 / 6 (50.00%)	2 / 3 (66.67%)	6 / 14 (42.86%)
occurrences (all)	5	2	8
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	5 / 14 (35.71%)
occurrences (all)	2	1	5
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	3 / 14 (21.43%)
occurrences (all)	1	0	4
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
nail loss			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
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subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Skin hypopigmentation subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 14 (0.00%) 0
skin ulceration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 14 (7.14%) 1
Renal and urinary disorders			
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 14 (7.14%) 1
Dysuria subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 14 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 14 (0.00%) 0
urinary disorders subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 3 (33.33%) 1	0 / 14 (0.00%) 0
Polyuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 14 (7.14%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 14 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 14 (7.14%) 1
Bone pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	2 / 14 (14.29%) 2
Myalgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	1 / 14 (7.14%) 1
Infections and infestations			

bronchial infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
gum infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nail infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 3 (66.67%)	1 / 14 (7.14%)
occurrences (all)	2	2	1
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
hypocalcemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
hypoglycemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Hypomagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Hypophosphataemia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported