



Clinical trial results:

Targeting Microenvironment and Cellular Immunity in Sarcomas Weekly trabectedin combined with Metronomic Cyclophosphamide in Patients with Advanced Pretreated Soft-tissue Sarcomas. A Phase I/II study from the French Sarcoma Group.

Summary

EudraCT number	2015-002760-16
Trial protocol	FR
Global end of trial date	15 September 2020

Results information

Result version number	v1 (current)
This version publication date	25 January 2026
First version publication date	25 January 2026

Trial information

Trial identification

Sponsor protocol code	IB2015-04
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02805725
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	27 January 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I:

To establish the recommended phase II dose (RP2D), the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D28), the safety profile, and the dose limiting toxicities (DLT) of trabectedin given in combination with cyclophosphamide (CP).

Phase II:

To evaluate the antitumor activity of trabectedin in association with CP in terms of non-progression at 6 months (complete or partial responses or stable disease more than 24 weeks, as per RECIST v1.1 criteria) after centralized radiological review, in patients with advanced STS who already failed anthracycline-containing chemotherapy (CT).

Protection of trial subjects:

A supervisory committee is constituted to evaluate the benefit/risk ratio along the study period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	27
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I (dose escalation study) : Over the period from December 2015 to February 2018, 20 patients were included. Phase II (all analysis) : Over the period from September 2018 to August 2019, 30 patients were included.

Pre-assignment

Screening details:

There were no screen failure in phase I and phase II.

Period 1

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

Blinding implementation details:

No blinding used.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)
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Arm description:

Trabectedin 0.30 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 1 of dose escalation.
Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.

Arm type	Experimental
Investigational medicinal product name	TRABECTEDIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administrated intraveinously on days 1, 8 and 15 of each cycle, every four weeks. It should be administered as a 3-hour IV infusion.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide (CP) will be administrated at a fixed dose of 50mg x b.i.d, twice a day (in the morning and evening) and on a one week on /one week off schedule.
CP should be taken fasting but may be given with food to improve digestive tolerance as no significant PK variation has been demonstrated in this regard. Since food does not either significantly affect the bioavailability of oral MT in adult patients, the drug may be taken regardless of meals.

Arm title	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)
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Arm description:

Trabectedin 0.40 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 2 of dose escalation.
Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.

Arm type	Experimental
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Investigational medicinal product name	TRABECTEDIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administrated intraveinously on days 1, 8 and 15 of each cycle, every four weeks. It should be administered as a 3-hour IV infusion.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide (CP) will be administrated at a fixed dose of 50mg x b.i.d, twice a day (in the morning and evening) and on a one week on /one week off schedule.

CP should be taken fasting but may be given with food to improve digestive tolerance as no significant PK variation has been demonstrated in this regard. Since food does not either significantly affect the bioavailability of oral MT in adult patients, the drug may be taken regardless of meals.

Arm title	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)
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Arm description:

Trabectedin 0.50 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 3 of dose escalation.

Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days

Arm type	Experimental
Investigational medicinal product name	TRABECTEDIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administrated intraveinously on days 1, 8 and 15 of each cycle, every four weeks. It should be administered as a 3-hour IV infusion.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide (CP) will be administrated at a fixed dose of 50mg x b.i.d, twice a day (in the morning and evening) and on a one week on /one week off schedule.

CP should be taken fasting but may be given with food to improve digestive tolerance as no significant PK variation has been demonstrated in this regard. Since food does not either significantly affect the bioavailability of oral MT in adult patients, the drug may be taken regardless of meals.

Arm title	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
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Arm description:

Trabectedin 0.60 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 4 of dose escalation.

Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.

Arm type	Experimental
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Investigational medicinal product name	TRABECTEDIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administrated intraveinously on days 1, 8 and 15 of each cycle, every four weeks. It should be administered as a 3-hour IV infusion.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide (CP) will be administrated at a fixed dose of 50mg x b.i.d, twice a day (in the morning and evening) and on a one week on /one week off schedule.

CP should be taken fasting but may be given with food to improve digestive tolerance as no significant PK variation has been demonstrated in this regard. Since food does not either significantly affect the bioavailability of oral MT in adult patients, the drug may be taken regardless of meals.

Arm title	Phase II - advanced STS
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Arm description:

Trabectedin 0.50 mg/m² will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in the phase II part of the study.

Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days

Phase 2: Trabectedin: All patients will be treated at the RP2D of trabectedin defined in the preliminary phase I trial with the same schedule as in the phase I trial.

Phase 2: Cyclophosphamide: All patients will be treated with metronomic cyclophosphamide with the same schedule as in the phase I trial.

Arm type	Experimental
Investigational medicinal product name	TRABECTEDIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administrated intraveinously on days 1, 8 and 15 of each cycle, every four weeks with a dose of 0.50mg/m². It should be administered as a 3-hour IV infusion.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide (CP) will be administrated at a fixed dose of 50mg x b.i.d, twice a day (in the morning and evening) and on a one week on /one week off schedule.

CP should be taken fasting but may be given with food to improve digestive tolerance as no significant PK variation has been demonstrated in this regard. Since food does not either significantly affect the bioavailability of oral MT in adult patients, the drug may be taken regardless of meals.

Number of subjects in period 1	Cohort 1: dose escalation - dose level 1 (0.30 mg/m ²)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m ²)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m ²)
Started	3	3	7
Completed	3	3	5
Not completed	0	0	2
Clinical progression	-	-	1
Adverse event, non-fatal	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort 4: dose escalation - dose level 4 (0.60 mg/m ²)	Phase II - advanced STS
Started	7	30
Completed	5	24
Not completed	2	6
Clinical progression	-	-
Adverse event, non-fatal	2	-
Protocol deviation	-	6

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)
Reporting group description: Trabectedin 0.30 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 1 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.	
Reporting group title	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)
Reporting group description: Trabectedin 0.40 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 2 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.	
Reporting group title	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)
Reporting group description: Trabectedin 0.50 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 3 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days	
Reporting group title	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Reporting group description: Trabectedin 0.60 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 4 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.	
Reporting group title	Phase II - advanced STS
Reporting group description: Trabectedin 0.50 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in the phase II part of the study. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days Phase 2: Trabectedin: All patients will be treated at the RP2D of trabectedin defined in the preliminary phase I trial with the same schedule as in the phase I trial. Phase 2: Cyclophosphamide: All patients will be treated with metronomic cyclophosphamide with the same schedule as in the phase I trial.	

Reporting group values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)
Number of subjects	3	3	7
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	1	5
From 65-84 years	0	2	2

85 years and over	0	0	0
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Age continuous Units: years arithmetic mean standard deviation	56.7 ± 9.3	63.3 ± 11.9	56.9 ± 11.1
Gender categorical Units: Subjects			
Female	2	3	2
Male	1	0	5
ECOG Units: Subjects			
ECOG = 0	1	2	2
ECOG = 1	2	0	5
ECOG = 2	0	0	0
ECOG = 3	0	0	0
ECOG = 4	0	0	0
Not available	0	1	0
ECG Units: Subjects			
Done	3	3	7
Not done	0	0	0
Not available	0	0	0
Concomitant treatment Units: Subjects			
No	0	0	1
Yes	3	3	6
Not available	0	0	0
Echocardiography : left ventricular ejection fraction (LVEF) Units: Subjects			
Done	0	0	7
Not done	3	3	0
Not available	0	0	0

Reporting group values	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)	Phase II - advanced STS	Total
Number of subjects	7	30	50
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)	5	13	27
From 65-84 years	2	17	23

85 years and over	0	0	0
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Age continuous Units: years arithmetic mean standard deviation	52.6 ± 15.7	61.5 ± 14.5	-
Gender categorical Units: Subjects			
Female	3	13	23
Male	4	17	27
ECOG Units: Subjects			
ECOG = 0	2	7	14
ECOG = 1	5	21	33
ECOG = 2	0	2	2
ECOG = 3	0	0	0
ECOG = 4	0	0	0
Not available	0	0	1
ECG Units: Subjects			
Done	7	26	46
Not done	0	4	4
Not available	0	0	0
Concomitant treatment Units: Subjects			
No	0	2	3
Yes	7	28	47
Not available	0	0	0
Echocardiography : left ventricular ejection fraction (LVEF) Units: Subjects			
Done	7	29	43
Not done	0	1	7
Not available	0	0	0

End points

End points reporting groups

Reporting group title	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)
Reporting group description: Trabectedin 0.30 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 1 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.	
Reporting group title	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)
Reporting group description: Trabectedin 0.40 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 2 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.	
Reporting group title	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)
Reporting group description: Trabectedin 0.50 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 3 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days	
Reporting group title	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Reporting group description: Trabectedin 0.60 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in cohort 4 of dose escalation. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days.	
Reporting group title	Phase II - advanced STS
Reporting group description: Trabectedin 0.50 mg/m2 will be administered intravenously (IV), 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks, in the phase II part of the study. Cyclophosphamide (CP) will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule. 1 cycle = 28 days Phase 2: Trabectedin: All patients will be treated at the RP2D of trabectedin defined in the preliminary phase I trial with the same schedule as in the phase I trial. Phase 2: Cyclophosphamide: All patients will be treated with metronomic cyclophosphamide with the same schedule as in the phase I trial.	

Primary: Dose escalation part : Maximum Tolerated Dose (MTD) of Trabectedin When Administered in Association with CP

End point title	Dose escalation part : Maximum Tolerated Dose (MTD) of Trabectedin When Administered in Association with CP ^[1] ^[2]
End point description: MTD was determined by testing increasing doses of trabectedin up to 0.60 mg/m2 via IV on dose escalation cohorts 1 to 4 with 3 to 6 participants each. The MTD is defined as the highest dose at which no more than 1 in 6 of the patients in the cohort experienced a DLT in the first treatment cycle. See subsequent primary outcome measure for the DLT definition. All phase I patients received Trabectedin IV (3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks) in combination with CP (bi-daily (50 mg x 2) and given on a week on/week off) according to the established dose escalation schedule. Patients who withdrew before completing the cycle 1 of treatment for other reason than DLT were not evaluable.	
End point type	Primary
End point timeframe: During the first cycle (28 days)	

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: MTD were assessed in the escalation part. 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: Maximum Tolerated Dose (MTD) was primary endpoint only for dose escalation cohort.

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m ²)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m ²)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m ²)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m ²)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: mg/m ²				
number (not applicable)	0.50	0.50	0.50	0.50

Statistical analyses

No statistical analyses for this end point

Primary: Dose escalation part : Number of patient who experienced Dose-Limiting Toxicities (DLTs)

End point title	Dose escalation part : Number of patient who experienced Dose-Limiting Toxicities (DLTs) ^{[3][4]}
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End point description:

A DLT was defined as a treatment-related (at least possibly related) adverse event using the CTCAE V4.0, occurring during the first cycle of treatment (28 days), that meets one of the following criteria:

- Any grade-4 toxicity (except for vomiting without maximal symptomatic/prophylactic treatment)
- Grade-3 non-haematological toxicity lasting > 7days (except for 1st episode of nausea without maximal symptomatic/ prophylactic treatment and if toxicity is transaminitis, which may last > 7 days if total bilirubin is normal or grade-1)
- Grade-3 hematologic toxicity lasting for > 7days
- Grade 4 neutropenia with fever
- Grade > 2 thrombocytopenia with bleeding
- Is unrelated to disease, disease progression, inter-current illness, or concomitant medications.

4 patients were not evaluable for DLT evaluation as they did not complete the DLT assessment period: 2 in cohort 3 and 2 in cohort 4.

End point type	Primary
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End point timeframe:

During the first cycle (28 days)

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: DLT were assessed in the escalation part. 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: Dose-Limiting Toxicities (DLTs) was primary endpoint only for dose escalation cohorts.

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: Participants				
number (not applicable)	0	0	0	2

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: Percentage of Patients in Non-progression at 6 months (RECIST V1.1)

End point title	Phase II: Percentage of Patients in Non-progression at 6 months (RECIST V1.1) ^{[5][6]}
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End point description:

Non-progression is defined as complete or partial response (CR, PR) or stable disease (SD), as per RECIST v1.1. According to RECIST v1.1: Complete Response (CR) is defined as disappearance of all target lesions; Partial Response (PR) is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at baseline (SSD); Stable disease (SD) is defined as Neither sufficient shrinkage (compared to baseline) to qualify for PR or CR nor sufficient increase (taking as reference the SSD or while on study, whichever is smallest) to qualify for progressive disease (PD).

End point type	Primary
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End point timeframe:

6 months after the start of treatment

Notes:

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

Justification: Only descriptive statistical analysis was performed for the primary endpoint.

[6] - 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: As non-progression at 6 months was primary endpoint for phase II cohort, only non-progression at 6 month for dose escalation parts was reported in this secondary endpoint.

End point values	Phase II - advanced STS			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Percentage of participants				
number (confidence interval 95%)	12.5 (2.7 to 32.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (RECIST V1.1)

End point title	Objective Response Rate (RECIST V1.1)
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End point description:

Objective response is defined as complete or partial response (CR, PR) as per RECIST v1.1. According to RECIST v1.1: Complete Response (CR) is defined as disappearance of all target lesions; Partial Response (PR) is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at baseline (SSD). This rate was calculated as the number of patients alive with complete or partial response (CR, PR) divided by the number of patients eligible and assessable for the safety analysis.

End point type	Secondary
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End point timeframe:

Throughout the treatment period, an average of 6 months.

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: Percentage of patients				
number (confidence interval 95%)	0 (0.0 to 0.0)	0 (0.0 to 0.0)	0 (0.0 to 0.0)	0 (0.0 to 0)

End point values	Phase II - advanced STS			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Percentage of patients				
number (confidence interval 95%)	8.3 (1.0 to 27.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival is defined as the time from the study initiation to death (any cause). Median overall survival was reported using kaplan-Meier method for calculation.

End point type	Secondary
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End point timeframe:

Overall Survival (OS)

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: Percentage of 1-year overall survival				
number (confidence interval 95%)	75 (46.3 to 89.8)	75 (46.3 to 89.8)	75 (46.3 to 89.8)	75 (46.3 to 89.8)

End point values	Phase II - advanced STS			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Percentage of 1-year overall survival				
number (confidence interval 95%)	52.4 (30.5 to 70.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	
Progression-free survival is defined as the time from study treatment initiation to disease progression or death (of any cause), whichever occurs first. Progression is defined using RECIST v1.1, as a 20% increase in the sum of diameters of target lesions (taking as reference the smallest sum on study), or a unequivocal progression of existing non-target lesions, or the appearance of one or more new lesions. Median PFS was reported using kaplan-Meier method for calculation. Median PFS was reported using kaplan-Meier method for calculation.	
End point type	Secondary
End point timeframe:	
From start of treatment, and during treatment until progression or death for any cause for up to 12 months.	

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: Percentage of 1-year progression-free				
number (confidence interval 95%)	6.3 (0.04 to 24.7)	6.3 (0.04 to 24.7)	6.3 (0.04 to 24.7)	6.3 (0.04 to 24.7)

End point values	Phase II - advanced STS			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Percentage of 1-year progression-free				
number (confidence interval 95%)	8.3 (1.4 to 23.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response under treatment

End point title	Objective response under treatment
End point description:	
Following RECIST v1.1 recommendations: * Objective response rate (ORR) is defined as the proportion of patients with complete or partial response (CR, PR) as per RECIST v1.1 criteria. * Objective response under treatment is recorded from study treatment initiation until the end of treatment and determined once all the data for the patient is known. * Claimed responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors. * Disease status under treatment, whatever the response observed, will be centrally reviewed for all patients, by an independent expert radiologist. Reviewed data will be used for the efficacy analysis.	
End point type	Secondary
End point timeframe:	
Objective response under treatment.	

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: Participants				
number (not applicable)	0	0	0	0

End point values	Phase II - advanced STS			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Participants				
number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Percentage of Patients in Non-progression at 6 months (RECIST V1.1)

End point title	Phase I: Percentage of Patients in Non-progression at 6 months (RECIST V1.1) ^[7]
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End point description:

Non-progression is defined as complete or partial response (CR, PR) or stable disease (SD), as per RECIST v1.1. According to RECIST v1.1: Complete Response (CR) is defined as disappearance of all target lesions; Partial Response (PR) is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at baseline (SSD); Stable disease (SD) is defined as Neither sufficient shrinkage (compared to baseline) to qualify for PR or CR nor sufficient increase (taking as reference the SSD or while on study, whichever is smallest) to qualify for progressive disease (PD)

End point type	Secondary
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End point timeframe:

6 months after the start of treatment

Notes:

[7] - 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: As non-progression at 6 months was primary endpoint for expansion cohort, only non-progression at 6 months for dose escalation part was reported in this secondary endpoint.

End point values	Cohort 1: dose escalation - dose level 1 (0.30 mg/m ²)	Cohort 2: dose escalation - dose level 2 (0.40 mg/m ²)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m ²)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m ²)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	5
Units: Percentage of patients				
number (confidence interval 95%)	12.5 (1.5 to 38.4)	12.5 (1.5 to 38.4)	12.5 (1.5 to 38.4)	12.5 (1.5 to 38.4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)
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Reporting group description: -

Reporting group title	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)
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Reporting group description: -

Reporting group title	Phase II - advanced STS
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Reporting group description: -

Reporting group title	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)
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Reporting group description: -

Reporting group title	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)
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Reporting group description: -

Serious adverse events	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Phase II - advanced STS
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	20 / 30 (66.67%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLEEDING OF TUMOR	Additional description: BLEEDING OF TUMOR		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
PULMONARY EMBOLISM	Additional description: PULMONARY EMBOLISM		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OCCLUSIVE THROMBUS OF CAELIAC TRUNK Additional description: OCCLUSIVE THROMBUS OF CAELIAC TRUNK			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPERIOR VEINA CAVA COMPRESSION Additional description: SUPERIOR VEINA CAVA COMPRESSION			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Surgical and medical procedures			
EXERESIS OF A PAINFUL NODULE OF THE RIGHT BUTTOCK Additional description: EXERESIS OF A PAINFUL NODULE OF THE RIGHT BUTTOCK			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DISEASE PROGRESSION Additional description: DISEASE PROGRESSION			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
OVERALL CONDITION DEGRADATION Additional description: OVERALL CONDITION DEGRADATION			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

PNEUMOTHORAX alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: PNEUMOTHORAX		
	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
	0 / 0	0 / 0	0 / 1
	0 / 0	0 / 0	0 / 0
PLEURAL PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: PLEURAL PAIN		
	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
	0 / 0	0 / 0	0 / 1
	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: PLEURAL EFFUSION		
	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
	0 / 0	0 / 1	0 / 0
	0 / 0	0 / 0	0 / 0
Investigations CPK INCREASE alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: CPK INCREASE		
	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
	0 / 0	0 / 0	1 / 1
	0 / 0	0 / 0	0 / 0
CPK INCREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: CPK INCREASED		
	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
GGT INCREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: GGT INCREASED		
	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
LYMPHOPENIA alternative assessment type: Non-systematic	Additional description: LYMPHOPENIA		

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA	Additional description: NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
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 DECREASE	Additional description: PLATELET DECREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOPENIA	Additional description: THROMBOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WORSENING OF GGT INCREASED	Additional description: WORSENING OF GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
DECOMPENSATION POST BIOPSY	Additional description: DECOMPENSATION POST BIOPSY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ARYTHMIA	Additional description: ARYTHMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEFT CARDIAC DECOMPENSATION	Additional description: LEFT CARDIAC DECOMPENSATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CRURALGIA	Additional description: CRURALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MEDULAR COMPRESSION	Additional description: MEDULAR COMPRESSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	4 / 30 (13.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMOTYPISIS	Additional description: HEMOTYPISIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE PANCYTOPENIA	Additional description: FEBRILE PANCYTOPENIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (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
WORSENING OF ANEMIA	Additional description: WORSENING OF ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ACUTE PANCREATITIS	Additional description: ACUTE PANCREATITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (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
OCCLUSIVE SYNDROM	Additional description: OCCLUSIVE SYNDROM		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
PYELOCALICIAL URETERO DILATION	Additional description: PYELOCALICIAL URETERO DILATION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
CHEST PAIN	Additional description: CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (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			
SEPTIC SHOCK	Additional description: SEPTIC SHOCK		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLEEDING OF TUMOR	Additional description: BLEEDING OF TUMOR		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
PULMONARY EMBOLISM	Additional description: PULMONARY EMBOLISM		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

OCCLUSIVE THROMBUS OF CAELIAC TRUNK		Additional description: OCCLUSIVE THROMBUS OF CAELIAC TRUNK	
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPERIOR VEINA CAVA COMPRESSION		Additional description: SUPERIOR VEINA CAVA COMPRESSION	
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
EXERESIS OF A PAINFUL NODULE OF THE RIGHT BUTTOCK		Additional description: EXERESIS OF A PAINFUL NODULE OF THE RIGHT BUTTOCK	
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
DISEASE PROGRESSION		Additional description: DISEASE PROGRESSION	
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVERALL CONDITION DEGRADATION		Additional description: OVERALL CONDITION DEGRADATION	
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PNEUMOTHORAX		Additional description: PNEUMOTHORAX	
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL PAIN	Additional description: PLEURAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION	Additional description: PLEURAL EFFUSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
CPK INCREASE	Additional description: CPK INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CPK INCREASED	Additional description: CPK INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT INCREASED	Additional description: GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA	Additional description: LYMPHOPENIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA	Additional description: NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET DECREASE	Additional description: PLATELET DECREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOPENIA	Additional description: THROMBOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WORSENING OF GGT INCREASED	Additional description: WORSENING OF GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
DECOMPENSATION POST BIOPSY	Additional description: DECOMPENSATION POST BIOPSY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ARYTHMIA	Additional description: ARYTHMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT CARDIAC DECOMPENSATION	Additional description: LEFT CARDIAC DECOMPENSATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CRURALGIA	Additional description: CRURALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MEDULAR COMPRESSION	Additional description: MEDULAR COMPRESSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMOTYPSIS	Additional description: HEMOTYPSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE PANCYTOPENIA	Additional description: FEBRILE PANCYTOPENIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WORSENING OF ANEMIA	Additional description: WORSENING OF ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ACUTE PANCREATITIS	Additional description: ACUTE PANCREATITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OCCLUSIVE SYNDROM	Additional description: OCCLUSIVE SYNDROM		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
PYELOCALICIAL URETERO DILATION	Additional description: PYELOCALICIAL URETERO DILATION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
CHEST PAIN	Additional description: CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
SEPTIC SHOCK	Additional description: SEPTIC SHOCK		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: dose escalation - dose level 1 (0.30 mg/m2)	Cohort 3: dose escalation - dose level 3 (0.50 mg/m2)	Phase II - advanced STS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	5 / 5 (100.00%)	30 / 30 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INTERMITTENT RIGHT ILIAC FOSSEA PAIN (TUMOR PAIN)	Additional description: INTERMITTENT RIGHT ILIAC FOSSEA PAIN (TUMOR PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
INTERMITTENT TUMORAL LEFT PECTORAL PAIN	Additional description: INTERMITTENT TUMORAL LEFT PECTORAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
RIGHT HYPOCHONDRIA PAIN	Additional description: RIGHT HYPOCHONDRIA PAIN		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
TUMOR PAIN	Additional description: TUMOR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
LEFT EYE PRE-THROMBOSIS	Additional description: LEFT EYE PRE-THROMBOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
LEFT ARM LYMPHEDEMA	Additional description: LEFT ARM LYMPHEDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
ASTHENIA	Additional description: ASTHENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	4 / 5 (80.00%)	17 / 30 (56.67%)
occurrences (all)	2	4	20
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	3 / 30 (10.00%)
occurrences (all)	1	0	3
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
GENERAL STATUT ALTERATION	Additional description: GENERAL STATUT ALTERATION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
INTERMITTENT ASTHENIA	Additional description: INTERMITTENT ASTHENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	4 / 30 (13.33%)
occurrences (all)	1	0	4
INFERIOR LIMB EDEMA	Additional description: INFERIOR LIMB EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
INTERMITTENT FEVER	Additional description: INTERMITTENT FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
INTERMITTENT EDEMA	Additional description: INTERMITTENT EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
INTERMITTENT INFERIOR LIMB EDEMA	Additional description: INTERMITTENT INFERIOR LIMB EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
INTERMITTENT LEFT ILIAC PAIN	Additional description: INTERMITTENT LEFT ILIAC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
INTERMITTENTE ASTHENIA	Additional description: INTERMITTENTE ASTHENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
INTERMITTENT THORACIC PAIN	Additional description: INTERMITTENT THORACIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

LEFT LEG EDEMA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LEFT LEG EDEMA		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
	Additional description: LEFT ELBOW PAIN		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
LEFT ELBOW PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1	0	0
	Additional description: NON CARDIAC THORACIC PAIN		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
	Additional description: SEGMENTECTOMY SCARE PAIN		
NON CARDIAC THORACIC PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
	0	1	0
	Additional description: SITE INJECTION ERYTHEMA		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
SEGMENTECTOMY SCARE PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DRY SKIN		
	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	0	0	0
	Additional description: ERYTHEMATO-VESICULAR ERUPTION (ZONA TYPE)		
	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
SITE INJECTION ERYTHEMA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0	1	0
	Additional description: HAND FOOT SKIN REACTION		
	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
	0	1	0
	Additional description: PRURITUS		
Social circumstances DRY SKIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)			
	Additional description: ERYTHEMATO-VESICULAR ERUPTION (ZONA TYPE)		
	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
	0	1	0
	Additional description: HAND FOOT SKIN REACTION		
ERYTHEMATO-VESICULAR ERUPTION (ZONA TYPE) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
	0	1	0
	Additional description: PRURITUS		
HAND FOOT SKIN REACTION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)			
PRURITUS alternative assessment type: Non-			

systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
TELANGIECTASIA	Additional description: TELANGIECTASIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
METRORRHAGIA	Additional description: METRORRHAGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
ALLERGIC RHINITIS	Additional description: ALLERGIC RHINITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	2 / 30 (6.67%)
occurrences (all)	1	2	2
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	3 / 5 (60.00%)	4 / 30 (13.33%)
occurrences (all)	1	3	4
INTERMITTENT DRY COUGH WITHOUT FEVER	Additional description: INTERMITTENT DRY COUGH WITHOUT FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
INTERMITTENT COUGH	Additional description: INTERMITTENT COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
RHINITIS	Additional description: RHINITIS		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
RHINOLALY	Additional description: RHINOLALY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
RIGHT PLEURAL EFFUSION	Additional description: RIGHT PLEURAL EFFUSION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
RIGHT PLEURODYNIA	Additional description: RIGHT PLEURODYNIA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
VESICULAR MURMUR DIMINUTION	Additional description: VESICULAR MURMUR DIMINUTION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
Psychiatric disorders			
ANXIETY	Additional description: ANXIETY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
ASAT INCREASE	Additional description: ASAT INCREASE		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	5 / 30 (16.67%)
occurrences (all)	0	0	5
ALAT INCREASE	Additional description: ALAT INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	7 / 30 (23.33%)
occurrences (all)	0	0	7
ALAT INCREASED	Additional description: ALAT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
ASAT INCREASED	Additional description: ASAT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
ALKALINE PHOSPHOKINASE	Additional description: ALKALINE PHOSPHOKINASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	Additional description: ASPARTATE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
CPK INCREASE	Additional description: CPK INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	4 / 30 (13.33%)
occurrences (all)	0	0	9
CPK INCREASED	Additional description: CPK INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
GGT INCREASE	Additional description: GGT INCREASE		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	5 / 30 (16.67%)
occurrences (all)	0	0	5
HYPERLEUKOCYTOSIS	Additional description: HYPERLEUKOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
GGT INCREASED	Additional description: GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
INTERMITTANT NEUTROPENIA	Additional description: INTERMITTANT NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
INTERMITTENT LYMPHOPENIA	Additional description: INTERMITTENT LYMPHOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	4 / 30 (13.33%)
occurrences (all)	0	2	4
INTERMITTENT MONOCYTOSIS	Additional description: INTERMITTENT MONOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
INTERMITTENT NEUTROPENIA	Additional description: INTERMITTENT NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
INTERMITTENT NEUTROPÉNIA	Additional description: INTERMITTENT NEUTROPÉNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
INTERMITTENT PAL INCREASED	Additional description: INTERMITTENT PAL INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

INTERMITTENT GGT INCREASE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT GGT INCREASE		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
INTERMITTENTE NEUTROPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENTE NEUTROPENIA		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	2 / 30 (6.67%) 2
INTERMITTENT THROMBOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT THROMBOPENIA		
	1 / 3 (33.33%) 1	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
LDH INCREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LDH INCREASED		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
LEUCOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LEUCOPENIA		
	1 / 3 (33.33%) 1	1 / 5 (20.00%) 1	3 / 30 (10.00%) 3
LYMPHOCYTS COUNT DECREASE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LYMPHOCYTS COUNT DECREASE		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
LYMPHOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LYMPHOPENIA		
	1 / 3 (33.33%) 1	3 / 5 (60.00%) 3	21 / 30 (70.00%) 21
NTERMITTENT LYMPHOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: NTERMITTENT LYMPHOPENIA		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
NEUTROPENIA alternative assessment type: Non-systematic	Additional description: NEUTROPENIA		

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	8 / 30 (26.67%)
occurrences (all)	0	0	11
PAL INCREASE	Additional description: PAL INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	4 / 30 (13.33%)
occurrences (all)	1	0	4
PLATELET DECREASED	Additional description: PLATELET DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
WHITE BLOOD CELL DECREASE	Additional description: WHITE BLOOD CELL DECREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
THROMBOPENIA	Additional description: THROMBOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	9 / 30 (30.00%)
occurrences (all)	0	2	14
Injury, poisoning and procedural complications			
LEFT ELBOW RADIOEPITHELITIS	Additional description: LEFT ELBOW RADIOEPITHELITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
LEFT ELBOW FRACTURE	Additional description: LEFT ELBOW FRACTURE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
RIGHT ANKLE SPRAIN	Additional description: RIGHT ANKLE SPRAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
TACHYCARDIA	Additional description: TACHYCARDIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Nervous system disorders			
CEPHALEA	Additional description: CEPHALEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
DYSGEUSIA	Additional description: DYSGEUSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
CRURALGIA	Additional description: CRURALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
INFERIOR LIMB DYSESTHESIA	Additional description: INFERIOR LIMB DYSESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
INTERMITTENT HEADACHE	Additional description: INTERMITTENT HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
INTERMITTENT PARESTHESIA	Additional description: INTERMITTENT PARESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
INTERMITTENT PARIETAL HEADACHE	Additional description: INTERMITTENT PARIETAL HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
RIGHT HAND NEUROPATHY	Additional description: RIGHT HAND NEUROPATHY		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
SOMNOLENCE	Additional description: SOMNOLENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	3 / 5 (60.00%)	16 / 30 (53.33%)
occurrences (all)	1	3	21
INTERMITTENT ANEMIA	Additional description: INTERMITTENT ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
INTERMITTENTE ANEMIA	Additional description: INTERMITTENTE ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
VERTIGO	Additional description: VERTIGO		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
CONJUNCTIVITIS	Additional description: CONJUNCTIVITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
DIPLOPIA	Additional description: DIPLOPIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

ABDOMINAL BLOATING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ABDOMINAL BLOATING		
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
ABDOMINAL PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ABDOMINAL PAIN		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	2 / 30 (6.67%) 2
ABDOMINAL PAIN DUE TO CONSTIPATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ABDOMINAL PAIN DUE TO CONSTIPATION		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
APHTA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: APHTA		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
CONSTIPATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: CONSTIPATION		
	1 / 3 (33.33%) 1	2 / 5 (40.00%) 2	11 / 30 (36.67%) 15
BUCCAL MYCOSIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BUCCAL MYCOSIS		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	2 / 30 (6.67%) 2
BLACK STOOLS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BLACK STOOLS		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
DIARRHEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DIARRHEA		
	2 / 3 (66.67%) 4	1 / 5 (20.00%) 1	4 / 30 (13.33%) 6
EPIGASTRIC PAIN alternative assessment type: Non-systematic	Additional description: EPIGASTRIC PAIN		

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
FOOD DISGUST	Additional description: FOOD DISGUST		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
GASTROESOPHAGEAL REFLUX	Additional description: GASTROESOPHAGEAL REFLUX		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
HEMORROIDS	Additional description: HEMORROIDS		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
HEMORRHOIDS	Additional description: HEMORRHOIDS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
GINGIVITIS	Additional description: GINGIVITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
EPIGASTRALGIA	Additional description: EPIGASTRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	3 / 30 (10.00%)
occurrences (all)	0	2	3
INTERMITTENT CONSTIPATION	Additional description: INTERMITTENT CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
HYPOCHONDRIA PAIN	Additional description: HYPOCHONDRIA PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

INTERMITTENT NAUSEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT NAUSEA		
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
INTERMITTENT VOMITING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT VOMITING		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
INTERMITTENT EPIGASTRALGIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT EPIGASTRALGIA		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
INTERMITTENT DIARRHEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT DIARRHEA		
	1 / 3 (33.33%) 2	0 / 5 (0.00%) 0	1 / 30 (3.33%) 1
INTERMITTENT MUCOSITIS ORAL alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT MUCOSITIS ORAL		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
INTERMITTENT NAUSEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT NAUSEA		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	2 / 30 (6.67%) 2
INTERMITTENTE NAUSEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENTE NAUSEA		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	4 / 30 (13.33%) 4
INTERMITTENT VOMITING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT VOMITING		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	4 / 30 (13.33%) 4
ORAL MUCOSITIS alternative assessment type: Non-systematic	Additional description: ORAL MUCOSITIS		

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
LINGUALE MUCOSITIS	Additional description: LINGUALE MUCOSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
ODYNOPHAGIA	Additional description: ODYNOPHAGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	4 / 5 (80.00%)	14 / 30 (46.67%)
occurrences (all)	2	5	19
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
LINGUAL MUCOSITIS	Additional description: LINGUAL MUCOSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
ORAL MYCOSIS	Additional description: ORAL MYCOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
SPASMODIC ABDOMINAL PAIN	Additional description: SPASMODIC ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
XEROSTOMIA	Additional description: XEROSTOMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

VOMITING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: VOMITING		
	0 / 3 (0.00%) 0	4 / 5 (80.00%) 6	11 / 30 (36.67%) 13
Hepatobiliary disorders CHOLESTASIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: CHOLESTASIS		
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	2 / 30 (6.67%) 2
Renal and urinary disorders ACUTE RENAL INSUFFICIENCY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) INTERMITENT HEMATURIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) RENAL INSUFFICIENCY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) RENAL CHRONIC INSUFFICIENCY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ACUTE RENAL INSUFFICIENCY		
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
	Additional description: INTERMITENT HEMATURIA		
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
	Additional description: RENAL INSUFFICIENCY		
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 2	0 / 30 (0.00%) 0
	Additional description: RENAL CHRONIC INSUFFICIENCY		
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 30 (0.00%) 0
	Additional description: ANTE-BRACHIAL FLEXION RESTRICTION		
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0	0 / 30 (0.00%) 0
	Additional description: INFERIOR LIMB MYALGIA		

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
JOINT LEFT KNEE PAIN	Additional description: JOINT LEFT KNEE PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
LEFT RIB PAIN (BONE PAIN)	Additional description: LEFT RIB PAIN (BONE PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
LEFT FLANK PAIN (MUSCLE PAIN)	Additional description: LEFT FLANK PAIN (MUSCLE PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
LUMBAGO	Additional description: LUMBAGO		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
MUSCULAR PAIN	Additional description: MUSCULAR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
MUSCULAR LOMBAR PAIN	Additional description: MUSCULAR LOMBAR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
RIGHT GONALGIA (JOINT PAIN)	Additional description: RIGHT GONALGIA (JOINT PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
PAIN THENHENAR HEMIN OF THE LEFT HAND.	Additional description: PAIN THENHENAR HEMIN OF THE LEFT HAND.		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

PARIETAL CHEST PAIN (MUSCLE PAIN) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: PARIETAL CHEST PAIN (MUSCLE PAIN)		
	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	0	0	0
Infections and infestations	Additional description: DENTAL ABSCESS		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
	Additional description: GENITAL HERPES		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
	Additional description: INFECTIOUS RHINITIS		
	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	0	0	0
	Additional description: LARYNGITIS		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
	Additional description: MOUTH CANDIDA		
	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	1	0	0
	Additional description: RHINOPHARINGITIS		
	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	0	0	0
	Additional description: RHINOPHARYNGITIS		
	2 / 3 (66.67%)	0 / 5 (0.00%)	0 / 30 (0.00%)
	2	0	0
	Additional description: SPHENOIDAL SINUSITIS		

systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
VIRAL RHINOPHARYNGITIS	Additional description: VIRAL RHINOPHARYNGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	11 / 30 (36.67%)
occurrences (all)	0	2	12
HYPOALBUMINEMIA	Additional description: HYPOALBUMINEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
HYPO ALBUMINEMIA	Additional description: HYPO ALBUMINEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
INTERMITTANT HYPOPHOSPHATEMIA	Additional description: INTERMITTANT HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
LOSS OF APPETIT	Additional description: LOSS OF APPETIT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2

Non-serious adverse events	Cohort 2: dose escalation - dose level 2 (0.40 mg/m2)	Cohort 4: dose escalation - dose level 4 (0.60 mg/m2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	5 / 5 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INTERMITTENT RIGHT ILIAC FOSSEA PAIN (TUMOR PAIN)	Additional description: INTERMITTENT RIGHT ILIAC FOSSEA PAIN (TUMOR PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT TUMORAL LEFT PECTORAL PAIN	Additional description: INTERMITTENT TUMORAL LEFT PECTORAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
RIGHT HYPOCHONDRIA PAIN	Additional description: RIGHT HYPOCHONDRIA PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
TUMOR PAIN	Additional description: TUMOR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LEFT EYE PRE-THROMBOSIS	Additional description: LEFT EYE PRE-THROMBOSIS		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LEFT ARM LYMPHEDEMA	Additional description: LEFT ARM LYMPHEDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
ASTHENIA	Additional description: ASTHENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3 (100.00%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	5 / 5 (100.00%)	
occurrences (all)	0	6	
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
GENERAL STATUT ALTERATION	Additional description: GENERAL STATUT ALTERATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT ASTHENIA	Additional description: INTERMITTENT ASTHENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INFERIOR LIMB EDEMA	Additional description: INFERIOR LIMB EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
INTERMITTENT FEVER	Additional description: INTERMITTENT FEVER		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT EDEMA	Additional description: INTERMITTENT EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT INFERIOR LIMB EDEMA	Additional description: INTERMITTENT INFERIOR LIMB EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT LEFT ILIAC PAIN	Additional description: INTERMITTENT LEFT ILIAC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
INTERMITTENTE ASTHENIA	Additional description: INTERMITTENTE ASTHENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT THORACIC PAIN	Additional description: INTERMITTENT THORACIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LEFT LEG EDEMA	Additional description: LEFT LEG EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LEFT ELBOW PAIN	Additional description: LEFT ELBOW PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
NON CARDIAC THORACIC PAIN	Additional description: NON CARDIAC THORACIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

SEGMENTECTOMY SCARE PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SEGMENTECTOMY SCARE PAIN		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
SITE INJECTION ERYTHEMA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SITE INJECTION ERYTHEMA		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
Social circumstances DRY SKIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DRY SKIN		
	0 / 3 (0.00%)	1 / 5 (20.00%)	
	0	1	
ERYTHEMATO-VESICULAR ERUPTION (ZONA TYPE) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ERYTHEMATO-VESICULAR ERUPTION (ZONA TYPE)		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
HAND FOOT SKIN REACTION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: HAND FOOT SKIN REACTION		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
PRURITUS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: PRURITUS		
	0 / 3 (0.00%)	1 / 5 (20.00%)	
	0	1	
TELANGIECTASIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: TELANGIECTASIA		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
Reproductive system and breast disorders METRORRHAGIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: METRORRHAGIA		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	

Respiratory, thoracic and mediastinal disorders			
ALLERGIC RHINITIS	Additional description: ALLERGIC RHINITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
INTERMITTENT DRY COUGH WITHOUT FEVER	Additional description: INTERMITTENT DRY COUGH WITHOUT FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT COUGH	Additional description: INTERMITTENT COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
RHINITIS	Additional description: RHINITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RHINOLALY	Additional description: RHINOLALY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RIGHT PLEURAL EFFUSION	Additional description: RIGHT PLEURAL EFFUSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
RIGHT PLEURODYNIA	Additional description: RIGHT PLEURODYNIA		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
VESICULAR MURMUR DIMINUTION	Additional description: VESICULAR MURMUR DIMINUTION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
Psychiatric disorders			
ANXIETY	Additional description: ANXIETY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
ASAT INCREASE	Additional description: ASAT INCREASE		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
ALAT INCREASE	Additional description: ALAT INCREASE		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
ALAT INCREASED	Additional description: ALAT INCREASED		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	2 / 5 (40.00%) 2	
ASAT INCREASED	Additional description: ASAT INCREASED		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
ALKALINE PHOSPHOKINASE	Additional description: ALKALINE PHOSPHOKINASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
ASPARTATE AMINOTRANSFERASE INCREASED	Additional description: ASPARTATE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
CPK INCREASE	Additional description: CPK INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
CPK INCREASED	Additional description: CPK INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
GGT INCREASE	Additional description: GGT INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPERLEUKOCYTOSIS	Additional description: HYPERLEUKOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
GGT INCREASED	Additional description: GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
INTERMITTANT NEUTROPENIA	Additional description: INTERMITTANT NEUTROPENIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT LYMPHOPENIA	Additional description: INTERMITTENT LYMPHOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT MONOCYTOSIS	Additional description: INTERMITTENT MONOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT NEUTROPENIA	Additional description: INTERMITTENT NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT NEUTROPÉNIA	Additional description: INTERMITTENT NEUTROPÉNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT PAL INCREASED	Additional description: INTERMITTENT PAL INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT GGT INCREASE	Additional description: INTERMITTENT GGT INCREASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENTE NEUTROPENIA	Additional description: INTERMITTENTE NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT THROMBOPENIA	Additional description: INTERMITTENT THROMBOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	

LDH INCREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LDH INCREASED	
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1
LEUCOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LEUCOPENIA	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
LYMPHOCYTS COUNT DECREASE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LYMPHOCYTS COUNT DECREASE	
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1
LYMPHOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LYMPHOPENIA	
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1
INTERMITTENT LYMPHOPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT LYMPHOPENIA	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
NEUTROPENIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: NEUTROPENIA	
	0 / 3 (0.00%) 0	2 / 5 (40.00%) 4
PAL INCREASE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: PAL INCREASE	
	0 / 3 (0.00%) 0	2 / 5 (40.00%) 2
PLATELET DECREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: PLATELET DECREASED	
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1
WHITE BLOOD CELL DECREASE alternative assessment type: Non-systematic	Additional description: WHITE BLOOD CELL DECREASE	

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
THROMBOPENIA	Additional description: THROMBOPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
LEFT ELBOW RADIOEPITHELITIS	Additional description: LEFT ELBOW RADIOEPITHELITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LEFT ELBOW FRACTURE	Additional description: LEFT ELBOW FRACTURE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
RIGHT ANKLE SPRAIN	Additional description: RIGHT ANKLE SPRAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
TACHYCARDIA	Additional description: TACHYCARDIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
CEPHALEA	Additional description: CEPHALEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
DYSGEUSIA	Additional description: DYSGEUSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
CRURALGIA	Additional description: CRURALGIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INFERIOR LIMB DYSESTHESIA	Additional description: INFERIOR LIMB DYSESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENT HEADACHE	Additional description: INTERMITTENT HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT PARESTHESIA	Additional description: INTERMITTENT PARESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT PARIETAL HEADACHE	Additional description: INTERMITTENT PARIETAL HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RIGHT HAND NEUROPATHY	Additional description: RIGHT HAND NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
SOMNOLENCE	Additional description: SOMNOLENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	2 / 5 (40.00%)	
occurrences (all)	2	2	
INTERMITTENT ANEMIA	Additional description: INTERMITTENT ANEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTENTE ANEMIA	Additional description: INTERMITTENTE ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
VERTIGO	Additional description: VERTIGO		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Eye disorders			
CONJUNCTIVITIS	Additional description: CONJUNCTIVITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
DIPLOPIA	Additional description: DIPLOPIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
ABDOMINAL BLOATING	Additional description: ABDOMINAL BLOATING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
ABDOMINAL PAIN DUE TO CONSTIPATION	Additional description: ABDOMINAL PAIN DUE TO CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
APHTA	Additional description: APHTA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
BUCCAL MYCOSIS	Additional description: BUCCAL MYCOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
BLACK STOOLS	Additional description: BLACK STOOLS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
EPIGASTRIC PAIN	Additional description: EPIGASTRIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
FOOD DISGUST	Additional description: FOOD DISGUST		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
GASTROESOPHAGEAL REFLUX	Additional description: GASTROESOPHAGEAL REFLUX		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
HEMORRHOIDS	Additional description: HEMORRHOIDS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	

HEMORRHOIDS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: HEMORRHOIDS	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
GINGIVITIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: GINGIVITIS	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
EPIGASTRALGIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: EPIGASTRALGIA	
	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1
INTERMITTENT CONSTIPATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT CONSTIPATION	
	0 / 3 (0.00%) 0	2 / 5 (40.00%) 2
HYPOCHONDRIA PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: HYPOCHONDRIA PAIN	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
INTERMITTENT NAUSEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT NAUSEA	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
INTERMITTENT VOMITING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT VOMITING	
	1 / 3 (33.33%) 1	0 / 5 (0.00%) 0
INTERMITTENT EPIGASTRALGIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INTERMITTENT EPIGASTRALGIA	
	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
INTERMITTENT DIARRHEA alternative assessment type: Non-systematic	Additional description: INTERMITTENT DIARRHEA	

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT MUCOSITIS ORAL	Additional description: INTERMITTENT MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT NAUSEA	Additional description: INTERMITTENT NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
INTERMITTENTE NAUSEA	Additional description: INTERMITTENTE NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INTERMITTENT VOMITING	Additional description: INTERMITTENT VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
ORAL MUCOSITIS	Additional description: ORAL MUCOSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LINGUALE MUCOSITIS	Additional description: LINGUALE MUCOSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
ODYNOPHAGIA	Additional description: ODYNOPHAGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	4 / 5 (80.00%)	
occurrences (all)	1	7	

MUCOSITIS ORAL alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: MUCOSITIS ORAL		
	1 / 3 (33.33%)	1 / 5 (20.00%)	
	1	1	
LINGUAL MUCOSITIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LINGUAL MUCOSITIS		
	1 / 3 (33.33%)	0 / 5 (0.00%)	
	1	0	
ORAL MYCOSIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ORAL MYCOSIS		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
SPASMODIC ABDOMINAL PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SPASMODIC ABDOMINAL PAIN		
	1 / 3 (33.33%)	0 / 5 (0.00%)	
	1	0	
XEROSTOMIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: XEROSTOMIA		
	2 / 3 (66.67%)	1 / 5 (20.00%)	
	2	1	
VOMITING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: VOMITING		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
Hepatobiliary disorders CHOLESTASIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: CHOLESTASIS		
	0 / 3 (0.00%)	0 / 5 (0.00%)	
	0	0	
Renal and urinary disorders ACUTE RENAL INSUFFICIENCY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ACUTE RENAL INSUFFICIENCY		
	0 / 3 (0.00%)	1 / 5 (20.00%)	
	0	1	
INTERMITENT HEMATURIA	Additional description: INTERMITENT HEMATURIA		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
RENAL INSUFFICIENCY	Additional description: RENAL INSUFFICIENCY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
RENAL CHRONIC INSUFFICIENCY	Additional description: RENAL CHRONIC INSUFFICIENCY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
ANTE-BRACHIAL FLEXION RESTRICTION	Additional description: ANTE-BRACHIAL FLEXION RESTRICTION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	
INFERIOR LIMB MYALGIA	Additional description: INFERIOR LIMB MYALGIA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
JOINT LEFT KNEE PAIN	Additional description: JOINT LEFT KNEE PAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
LEFT RIB PAIN (BONE PAIN)	Additional description: LEFT RIB PAIN (BONE PAIN)		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
LEFT FLANK PAIN (MUSCLE PAIN)	Additional description: LEFT FLANK PAIN (MUSCLE PAIN)		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	
LUMBAGO	Additional description: LUMBAGO		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
MUSCULAR PAIN	Additional description: MUSCULAR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
MUSCULAR LOMBAR PAIN	Additional description: MUSCULAR LOMBAR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RIGHT GONALGIA (JOINT PAIN)	Additional description: RIGHT GONALGIA (JOINT PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
PAIN THENHENAR HEMIN OF THE LEFT HAND.	Additional description: PAIN THENHENAR HEMIN OF THE LEFT HAND.		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
PARIETAL CHEST PAIN (MUSCLE PAIN)	Additional description: PARIETAL CHEST PAIN (MUSCLE PAIN)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Infections and infestations			
DENTAL ABSCESS	Additional description: DENTAL ABSCESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
GENITAL HERPES	Additional description: GENITAL HERPES		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
INFECTIOUS RHINITIS	Additional description: INFECTIOUS RHINITIS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
LARYNGITIS	Additional description: LARYNGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
MOUTH CANDIDA	Additional description: MOUTH CANDIDA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
RHINOPHARINGITIS	Additional description: RHINOPHARINGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RHINOPHARYNGITIS	Additional description: RHINOPHARYNGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
SPHENOIDAL SINUSITIS	Additional description: SPHENOIDAL SINUSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
VIRAL RHINOPHARYNGITIS	Additional description: VIRAL RHINOPHARYNGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	
occurrences (all)	1	2	
HYPOALBUMINEMIA	Additional description: HYPOALBUMINEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
HYPO ALBUMINEMIA	Additional description: HYPO ALBUMINEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INTERMITTANT HYPOPHOSPHATEMIA	Additional description: INTERMITTANT HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
LOSS OF APPETIT	Additional description: LOSS OF APPETIT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2016	Protocol V2 dated 20-Jan-2016
28 October 2016	Protocol V3 dated 28-Oct-2016
26 April 2017	Protocol V4 dated 26-Apr-2017
19 October 2017	Protocol V5 dated 19-Oct-2017
11 December 2018	Protocol V6 dated 11-Dec-2018

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported