

**Clinical trial results:****A Phase I/II study of safety and efficacy of ribociclib (LEE011) in combination with trametinib (TMT212) in patients with metastatic or advanced solid tumors****Summary**

EudraCT number	2015-005019-34
Trial protocol	NL BE ES
Global end of trial date	24 September 2019

Results information

Result version number	v1 (current)
This version publication date	23 September 2020
First version publication date	23 September 2020

Trial information**Trial identification**

Sponsor protocol code	CTMT212X2106
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02703571
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Phase Ib was to define the maximum tolerated dose (MTD) and/or the recommended Phase II regimen (RP2R) of ribociclib and trametinib in patients with solid tumors. The Phase II part was not pursued, and the study was closed after completion of the Phase Ib part of the study.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Australia: 7
Worldwide total number of subjects	95
EEA total number of subjects	32

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)	66
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 15 investigative sites in 7 countries from 29-Jun-2016 to 14-Mar-2019

Pre-assignment

Screening details:

Subjects with advanced or metastatic solid tumors independently of the RAS mutation status were screened for eligibility during the 28 days prior to starting study treatment on Cycle 1 Day 1. The eligibility assessments were performed and ensured that all inclusion and exclusion were satisfied.

Period 1

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

Arms

Arm title	TMT212+LEE011
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Arm description:

Phase Ib part: Patients with advanced or metastatic solid tumors participating in the Phase I part received combination treatment with ribociclib (projected dose levels: 0.5 mg, 1 mg, 1.5 mg and 2 mg) and trametinib (projected dose levels: 200 mg, 300 mg, 400 mg, 500 mg and 600 mg) at different dosing regimens.

Phase II part: Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS mutant colorectal carcinoma who have failed at least two prior lines of treatment.

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

During the Phase I part, ribociclib was administered orally and escalated from 200 to 600mg at different dosing schedules: 1) once daily on days 1 to 21 of a 28 days cycle; 2) once daily on days 8 to 21 of a 21-day cycle (Schedule 1); and 3) once daily on days 1 to 14 of a 21-day cycle (Schedule 2).

Investigational medicinal product name	Trametinib
Investigational medicinal product code	TMT212
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the Phase I part, trametinib 0.5, 1, 1.5 or 2 mg was administered orally at different dosing schedules: 1) once daily on days 1 to 21 of a 28-day cycle; 2) once daily on days 1 to 14 of a 21-day cycle (Schedule 1 and Schedule 2)

Number of subjects in period 1	TMT212+LEE011
Started	95
Full analysis set	95
Safety set	95
Dose determining set	79
Completed	0
Not completed	95
Adverse event, serious fatal	1
Physician decision	8
Disease progression	55
Adverse event, non-fatal	14
Lost to follow-up	1
Sponsor decision	1
Subject/guardian decision	15

Baseline characteristics

Reporting groups

Reporting group title	Overall study
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Reporting group description:

Patients with advanced or metastatic solid tumors participating in the Phase I part received combination treatment with ribociclib (projected dose levels: 0.5 mg, 1 mg, 1.5 mg and 2 mg) and trametinib (projected dose levels: 200 mg, 300 mg, 400 mg, 500 mg and 600 mg) at different dosing regimens. Phase II part of the study was not conducted

Reporting group values	Overall study	Total	
Number of subjects	95	95	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	66	66	
From 65-84 years	29	29	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	58.0	-	
standard deviation	± 9.89	-	
Sex: Female, Male			
Units: Participants			
Female	46	46	
Male	49	49	
Race/Ethnicity, Customized			
Units: Subjects			
Asian	5	5	
Black	2	2	
Caucasian	84	84	
Pacific islander	1	1	
Unknown	3	3	

End points

End points reporting groups

Reporting group title	TMT212+LEE011
Reporting group description:	
Phase Ib part: Patients with advanced or metastatic solid tumors participating in the Phase I part received combination treatment with ribociclib (projected dose levels: 0.5 mg, 1 mg, 1.5 mg and 2 mg) and trametinib (projected dose levels: 200 mg, 300 mg, 400 mg, 500 mg and 600 mg) at different dosing regimens.	
Phase II part: Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS mutant colorectal carcinoma who have failed at least two prior lines of treatment.	

Primary: Phase Ib: Number of participants with dose limiting toxicities (DLTs)

End point title	Phase Ib: Number of participants with dose limiting toxicities (DLTs) ^[1]
End point description:	
Phase Ib part: Incidence of DLTs during the first 21 days of therapy. A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle of treatment with ribociclib and trametinib and meets any of the criteria described in the protocol.	
End point type	Primary
End point timeframe:	
21-day cycle one of treatment	

Notes:

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

Justification: No statistical analyses were planned for this endpoint

End point values	TMT212+LEE011			
	1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Participants	12			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: Objective Response Rate (ORR)

End point title	Phase II: Objective Response Rate (ORR) ^[2]
End point description:	
Phase II part: ORR is defined as the proportion of patients with a best overall confirmed complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by investigator assessment.	
End point type	Primary
End point timeframe:	
Until progression of disease up to 1 year	

Notes:

[2] - 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: No statistical analyses were planned for this endpoint

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[3]			
Units: Percentage of participants				
number (confidence interval 95%)	(to)			

Notes:

[3] - Phase 2 was not initiated; no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Progression disease rate

End point title	Phase Ib: Progression disease rate
End point description:	Phase Ib part: Progression disease rate defined as the proportion of patients with a progression disease as assessed per RECIST 1.1 by investigator assessment.
End point type	Secondary
End point timeframe:	Until progression of disease, up to approximately 2 years

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: Percentage of Participants				
number (confidence interval 95%)	44.2 (34.0 to 54.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Progression free survival (PFS)

End point title	Phase Ib: Progression free survival (PFS)
End point description:	Phase Ib part: PFS is defined as the time from the date of the first dose of study drug to the date of first documented disease progression per RECIST 1.1 and investigator assessment or death due to any cause.
End point type	Secondary
End point timeframe:	Until progression of disease or death, up to approximately 2 years

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: Months				
median (confidence interval 95%)	2.6 (1.8 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Duration of response (DOR)

End point title	Phase II: Duration of response (DOR)
End point description:	
Phase II part: Among patients with a confirmed response (PR or CR) per RECIST 1.1, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause.	
End point type	Secondary
End point timeframe:	
From first documented response until progression of disease or death, up to 1 year	

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[4]			
Units: Months				
arithmetic mean (confidence interval 95%)	(to)			

Notes:

[4] - Phase 2 was not initiated; no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Time to response

End point title	Phase II: Time to response
End point description:	
Phase II part: Time to overall response of CR or PR (TTR) is defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently) for patients with a confirmed CR or PR.	
Phase 2 was not initiated; no data was collected.	
End point type	Secondary

End point timeframe:

From start of study drug to first documented response, up to 1 year

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[5]			
Units: Months				
arithmetic mean (confidence interval 95%)	(to)			

Notes:

[5] - Phase 2 was not initiated; no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Disease Control Rate (DCR)

End point title	Phase II: Disease Control Rate (DCR)
End point description:	Phase II part: DCR is defined as the proportion of patients with best overall response of CR, PR, or SD per RECIST 1.1. Phase 2 was not initiated; no data was collected.
End point type	Secondary
End point timeframe:	Until progression of disease up to 1 year

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[6]			
Units: Percentage of Participants				
number (confidence interval 95%)	(to)			

Notes:

[6] - Phase 2 was not initiated; no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Progression Free Survival (PFS)

End point title	Phase II: Progression Free Survival (PFS)
End point description:	Phase II part: PFS is defined as the time from the date of the first dose of study drug to the date of first documented disease progression per RECIST 1.1 and investigator assessment or death due to any cause. Phase 2 was not initiated; no data was collected.
End point type	Secondary

End point timeframe:

Until progression of disease or death, up to 1 year

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[7]			
Units: Months				
median (confidence interval 95%)	(to)			

Notes:

[7] - Phase 2 was not initiated; no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Overall Survival (OS)

End point title	Phase II: Overall Survival (OS)
End point description:	Phase II part: OS is defined as the time from the date of first dose of study drug to the date of death due to any cause. Phase 2 was not initiated; no data was collected.
End point type	Secondary
End point timeframe:	Up to 1 year

End point values	TMT212+LEE01 1			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[8]			
Units: Months				
median (confidence interval 95%)	(to)			

Notes:

[8] - Phase 2 was not initiated; no data was collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 25.53 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Cohort 0: LEE011 200mg 21 on/7 off + TMT212 2 mg QD
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Reporting group description:

2 mg TMT212 administered once daily on Days 1-28 and 200 mg LEE011 administered once daily on Days 1-21 followed by a 7-day break of a 28-day cycle

Reporting group title	Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedule 1
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Reporting group description:

1.5 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle.

Reporting group title	Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD- Schedule 1
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Reporting group description:

2 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedule 1
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Reporting group description:

1.5 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedule 1
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Reporting group description:

2 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedule 1
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Reporting group description:

1.5 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedule 1
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Reporting group description:

2 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedule 2
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Reporting group description:

2 mg TMT212 administered once daily on Days 1-14 and LEE011 administered once daily on Days 1-14 of a 21-day cycle

Reporting group title	Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedule 1
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Reporting group description:

2 mg TMT212 administered once daily on Days 1-14 and 500 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedule 1
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Reporting group description:

1 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedule 1
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Reporting group description:

1 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle

Reporting group title	All Subjects
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Reporting group description:

All subjects who received at least one dose of either study drug in the Phase I part of the study

Serious adverse events	Cohort 0: LEE011 200mg 21 on/7 off + TMT212 2 mg QD	Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedule 1	Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD- Schedule 1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Pyrexia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Pharyngeal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Occult blood positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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			
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
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 perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Intestinal perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Obstruction gastric			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Pancreatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Cholangitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Hepatotoxicity			

subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Groin pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Biliary tract infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (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
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedule 1	Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedule 1	Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedule 1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	5 / 12 (41.67%)	4 / 12 (33.33%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	1	0
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Pyrexia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Pharyngeal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (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
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Occult blood positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (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
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Gastrointestinal perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Nausea			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Pancreatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 5 (20.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Cholangitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Hepatotoxicity			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Groin pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Biliary tract infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (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
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedule 1	Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedule 2	Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedule 1
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	6 / 9 (66.67%)	5 / 10 (50.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Pharyngeal inflammation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Occult blood positive			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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			
Overdose			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Presyncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (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
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Gastrointestinal perforation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Intestinal perforation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Nausea			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Obstruction gastric			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (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
Oesophagitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (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
Cholangitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (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
Groin pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (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			
Abdominal sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Biliary tract infection			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Rash pustular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedule 1	Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedule 1	All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	6 / 9 (66.67%)	40 / 95 (42.11%)
number of deaths (all causes)	0	2	8
number of deaths resulting from adverse events	0	0	1
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
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 physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal inflammation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Occult blood positive			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Haemorrhage intracranial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Presyncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	3 / 95 (3.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Gastrointestinal perforation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	3 / 95 (3.16%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	6 / 95 (6.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Biliary tract infection			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pustular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 0: LEE011 200mg 21 on/7 off + TMT212 2 mg QD	Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedule 1	Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD - Schedule 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	7 / 7 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pyogenic granuloma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypertension			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 7 (28.57%) 2	0 / 6 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Lymphoedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Vascular rupture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
General disorders and administration site conditions			
Chills subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 7 (28.57%) 2	0 / 6 (0.00%) 0
Device related thrombosis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Face oedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3	5 / 7 (71.43%) 5	3 / 6 (50.00%) 3
Gait disturbance subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Non-cardiac chest pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	1	4
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 7 (42.86%)	1 / 6 (16.67%)
occurrences (all)	1	5	1
Secretion discharge			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Suprapubic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Xerosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Immune system disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Pelvic pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Scrotal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Uterine pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Aphonia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1
Dysphonia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Dyspnoea			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Dyspnoea at rest			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Increased upper airway secretion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pleuritic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Productive cough			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Bruxism subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Confusional state subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Mental status changes subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Investigations			
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Alanine aminotransferase increased			

subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	3
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	4 / 6 (66.67%)
occurrences (all)	2	2	5
Bilirubin conjugated increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	2 / 6 (33.33%)
occurrences (all)	0	3	2
Blood bilirubin increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood creatine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 5 (40.00%)	3 / 7 (42.86%)	3 / 6 (50.00%)
occurrences (all)	2	3	4
Blood creatinine decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	3
Blood urea increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	1	1	2
International normalised ratio increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Liver function test increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Monocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Neutrophil count increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			

subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 2	0 / 6 (0.00%) 0
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Avulsion fracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Fracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Thermal burn subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Wrist fracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Cardiac disorders			
Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Mitral valve thickening			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ventricular arrhythmia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)	2 / 7 (28.57%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Neuropathy peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Seizure			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tongue paralysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Transient ischaemic attack			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 5 (60.00%)	2 / 7 (28.57%)	3 / 6 (50.00%)
occurrences (all)	4	3	3
Leukopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutropenia			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Ear and labyrinth disorders			
Ear congestion subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Eye disorders			
Chorioretinopathy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Eye irritation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Retinal detachment			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Retinal disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Retinal exudates			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Subretinal fluid			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	3 / 7 (42.86%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Abdominal pain lower			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0

Anal incontinence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)	5 / 7 (71.43%)	2 / 6 (33.33%)
occurrences (all)	3	12	6
Dry mouth			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Duodenal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Intra-abdominal haematoma subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Lip dry subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Lip pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Lip swelling subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 7 (42.86%) 6	4 / 6 (66.67%) 5
Oesophageal discomfort subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Oesophagitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Oral discomfort subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Proctalgia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Retching subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0

Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	3 / 6 (50.00%)
occurrences (all)	0	2	6
Tongue discolouration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tooth loss			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	5 / 7 (71.43%)	3 / 6 (50.00%)
occurrences (all)	2	6	7
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatosplenomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Dermatitis acneiform			
subjects affected / exposed	2 / 5 (40.00%)	3 / 7 (42.86%)	3 / 6 (50.00%)
occurrences (all)	2	13	4
Dry skin			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Eczema asteatotic			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Pain of skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	3 / 6 (50.00%)
occurrences (all)	0	3	7
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Rash pruritic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin burning sensation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin necrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chronic kidney disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Proteinuria			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle tightness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Myositis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Catheter site cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Erysipelas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Postoperative wound infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Staphylococcal skin infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Tinea cruris subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Tooth infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Viral infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Metabolism and nutrition disorders			
Appetite disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 7 (28.57%) 2	0 / 6 (0.00%) 0
Dehydration subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0
Hyperglycaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 7 (28.57%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedule 1	Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedule 1	Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedule 1
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 5 (100.00%)	12 / 12 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Pyogenic granuloma subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Tumour pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 12 (0.00%) 0	2 / 12 (16.67%) 2
Vascular disorders Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Embolism subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 2	0 / 12 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Lymphoedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Vascular rupture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	1 / 12 (8.33%) 1
Device related thrombosis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	4 / 5 (80.00%)	8 / 12 (66.67%)	7 / 12 (58.33%)
occurrences (all)	4	9	7
Gait disturbance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 5 (20.00%)	5 / 12 (41.67%)	5 / 12 (41.67%)
occurrences (all)	1	7	6
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	4 / 12 (33.33%)	3 / 12 (25.00%)
occurrences (all)	1	4	3
Secretion discharge			

subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Suprapubic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Xerosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Immune system disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Breast pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Scrotal pain			

subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Uterine pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Dysphonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)	3 / 12 (25.00%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Dyspnoea at rest			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Increased upper airway secretion			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Bruxism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mental status changes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	3	2	3
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 5 (80.00%)	5 / 12 (41.67%)	4 / 12 (33.33%)
occurrences (all)	5	6	4
Bilirubin conjugated increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 5 (40.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	2	4	1
Blood bilirubin increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood creatine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 5 (20.00%)	6 / 12 (50.00%)	6 / 12 (50.00%)
occurrences (all)	1	10	6
Blood creatinine decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	2	3
Blood urea increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
International normalised ratio increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lipase increased			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	1 / 12 (8.33%) 1
Liver function test increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Monocyte count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	4 / 12 (33.33%) 6	0 / 12 (0.00%) 0
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 2	2 / 12 (16.67%) 2
Weight decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	3 / 12 (25.00%) 4
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Avulsion fracture			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Fracture			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Thermal burn			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Wrist fracture			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Bradycardia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Mitral valve thickening			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Sinus bradycardia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Tachycardia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Ventricular arrhythmia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Nervous system disorders			
Ataxia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Balance disorder			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	2 / 5 (40.00%)	1 / 12 (8.33%)	2 / 12 (16.67%)
occurrences (all)	2	1	2
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	1 / 5 (20.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Hyperaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	3 / 12 (25.00%)
occurrences (all)	0	3	3
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Taste disorder			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 2	0 / 12 (0.00%) 0
Tongue paralysis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Transient ischaemic attack subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 3	8 / 12 (66.67%) 9	7 / 12 (58.33%) 9
Leukopenia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Lymphopenia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 12 (25.00%) 5	1 / 12 (8.33%) 2
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 12 (16.67%) 2	0 / 12 (0.00%) 0
Ear and labyrinth disorders			
Ear congestion subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Eye disorders			

Chorioretinopathy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye irritation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Retinal detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Retinal disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Retinal exudates			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Subretinal fluid			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1

Vitreous floaters subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Anal incontinence subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Ascites subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	1 / 12 (8.33%) 1	2 / 12 (16.67%) 2
Diarrhoea subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3	6 / 12 (50.00%) 6	7 / 12 (58.33%) 10
Dry mouth			

subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Duodenal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lip pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lip swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			

subjects affected / exposed	3 / 5 (60.00%)	7 / 12 (58.33%)	7 / 12 (58.33%)
occurrences (all)	3	10	8
Oesophageal discomfort			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oral discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	2 / 5 (40.00%)	8 / 12 (66.67%)	3 / 12 (25.00%)
occurrences (all)	2	12	3
Tongue discolouration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth loss			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vomiting			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	3 / 12 (25.00%) 10	5 / 12 (41.67%) 5
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hepatosplenomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Dermatitis acneiform			
subjects affected / exposed	1 / 5 (20.00%)	4 / 12 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	4	2
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	4 / 12 (33.33%)
occurrences (all)	0	2	4
Eczema asteatotic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 5 (20.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ingrowing nail			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain of skin			

subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Rash			
subjects affected / exposed	1 / 5 (20.00%)	8 / 12 (66.67%)	8 / 12 (66.67%)
occurrences (all)	2	16	10
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin burning sensation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Skin fissures			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Skin necrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Chronic kidney disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Micturition urgency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	4 / 12 (33.33%)
occurrences (all)	0	1	4
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Arthritis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Muscle swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Myositis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Neck pain			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Pain in extremity subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Infections and infestations			
Arthritis infective subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Catheter site cellulitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Erysipelas subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Eye infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Fungal infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Herpes simplex subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Localised infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Paronychia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0

Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Postoperative wound infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pustule			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tinea cruris			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Viral infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Metabolism and nutrition disorders			
Appetite disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Decreased appetite subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	3 / 12 (25.00%) 4	3 / 12 (25.00%) 3
Dehydration subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1	2 / 12 (16.67%) 2
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Hyperphosphataemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	3 / 12 (25.00%) 4	4 / 12 (33.33%) 4
Hypocalcaemia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)	4 / 12 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	6	3
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedule 1	Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedule 2	Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedule 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	8 / 9 (88.89%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pyogenic granuloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Embolism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Hypertension			
subjects affected / exposed	3 / 10 (30.00%)	0 / 9 (0.00%)	2 / 10 (20.00%)
occurrences (all)	3	0	2
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Lymphoedema			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Vascular rupture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
Device related thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	6 / 10 (60.00%)	4 / 9 (44.44%)	5 / 10 (50.00%)
occurrences (all)	7	5	6
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	5 / 10 (50.00%)	3 / 9 (33.33%)	1 / 10 (10.00%)
occurrences (all)	6	3	1
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 9 (33.33%)	3 / 10 (30.00%)
occurrences (all)	2	3	3
Secretion discharge			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Suprapubic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Temperature intolerance			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Xerosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Immune system disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Pelvic pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Scrotal pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Uterine pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Respiratory, thoracic and mediastinal disorders			
Aphonia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0
Dysphonia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Dyspnoea			

subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Dyspnoea at rest			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Increased upper airway secretion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pharyngeal inflammation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pleuritic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Productive cough			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 10 (20.00%) 2
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Bruxism subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	1 / 10 (10.00%) 1
Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Mental status changes subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Sleep disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Investigations			
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Alanine aminotransferase increased			

subjects affected / exposed	2 / 10 (20.00%)	4 / 9 (44.44%)	2 / 10 (20.00%)
occurrences (all)	2	12	3
Amylase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	3	2
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 10 (70.00%)	5 / 9 (55.56%)	4 / 10 (40.00%)
occurrences (all)	8	8	6
Bilirubin conjugated increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	3
Blood bilirubin increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Blood creatine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 10 (40.00%)	4 / 9 (44.44%)	5 / 10 (50.00%)
occurrences (all)	6	8	7
Blood creatinine decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	0	3	3
Blood urea increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	1	6	3
Liver function test increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Monocyte count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	3	1	1
Neutrophil count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	2 / 10 (20.00%) 2
Weight decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	3 / 10 (30.00%) 4
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Avulsion fracture subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Thermal burn subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Wrist fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Cardiac disorders			
Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Mitral valve thickening			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Ventricular arrhythmia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Nervous system disorders			
Ataxia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Balance disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	1 / 10 (10.00%) 1
Dysgeusia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 9 (0.00%) 0	1 / 10 (10.00%) 2
Headache subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Hyperaesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 2
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0

Paraesthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Taste disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tongue paralysis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Transient ischaemic attack			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 10 (30.00%)	5 / 9 (55.56%)	3 / 10 (30.00%)
occurrences (all)	3	8	3
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Lymphopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neutropenia			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 9 (22.22%) 3	3 / 10 (30.00%) 6
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	3 / 9 (33.33%) 4	4 / 10 (40.00%) 7
Ear and labyrinth disorders			
Ear congestion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Eye disorders			
Chorioretinopathy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Eye irritation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Periorbital oedema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Retinal detachment			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Retinal disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Retinal exudates			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Subretinal fluid			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	3 / 9 (33.33%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
Abdominal pain lower			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Anal incontinence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	3 / 10 (30.00%)	2 / 9 (22.22%)	0 / 10 (0.00%)
occurrences (all)	3	2	0
Diarrhoea			
subjects affected / exposed	4 / 10 (40.00%)	5 / 9 (55.56%)	9 / 10 (90.00%)
occurrences (all)	6	6	13
Dry mouth			
subjects affected / exposed	3 / 10 (30.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	3	3	1
Duodenal ulcer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Intra-abdominal haematoma subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Lip dry subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Lip pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Lip swelling subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	3 / 9 (33.33%) 5	5 / 10 (50.00%) 6
Oesophageal discomfort subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Oesophagitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Oral discomfort subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Proctalgia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Retching subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0

Stomatitis			
subjects affected / exposed	3 / 10 (30.00%)	5 / 9 (55.56%)	6 / 10 (60.00%)
occurrences (all)	3	7	6
Tongue discolouration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tooth loss			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 10 (30.00%)	5 / 9 (55.56%)	2 / 10 (20.00%)
occurrences (all)	3	8	2
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hepatosplenomegaly			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	3 / 10 (30.00%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	4	1	2
Dry skin			
subjects affected / exposed	3 / 10 (30.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Eczema asteatotic			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Photosensitivity reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	4 / 10 (40.00%)	2 / 9 (22.22%)	2 / 10 (20.00%)
occurrences (all)	4	2	2
Rash			
subjects affected / exposed	4 / 10 (40.00%)	5 / 9 (55.56%)	7 / 10 (70.00%)
occurrences (all)	6	13	8
Rash macular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Rash maculo-papular			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1

Rash pruritic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin necrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Chronic kidney disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hydronephrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Proteinuria			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 2
Renal failure subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Arthritis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Flank pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Groin pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Muscle swelling subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Muscle tightness			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Myositis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catheter site cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Erysipelas			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Postoperative wound infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Staphylococcal skin infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Tinea cruris subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Tooth infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 3	1 / 10 (10.00%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	1 / 10 (10.00%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Metabolism and nutrition disorders			
Appetite disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 9 (22.22%) 2	1 / 10 (10.00%) 1
Dehydration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 9 (22.22%) 2	2 / 10 (20.00%) 3
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Hyperglycaemia			

subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	2 / 10 (20.00%)
occurrences (all)	3	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Hyperphosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 10 (20.00%)	4 / 9 (44.44%)	4 / 10 (40.00%)
occurrences (all)	2	5	4
Hypocalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedule 1	Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedule 1	All Subjects
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 10 (100.00%)	9 / 9 (100.00%)	94 / 95 (98.95%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Pyogenic granuloma subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Tumour pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	4 / 95 (4.21%) 4
Vascular disorders Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Embolism subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	1 / 95 (1.05%) 1
Hypertension subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	11 / 95 (11.58%) 12
Hypotension subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	3 / 95 (3.16%) 3
Lymphoedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Vascular rupture subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	8 / 95 (8.42%) 10
Device related thrombosis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	5 / 10 (50.00%)	4 / 9 (44.44%)	54 / 95 (56.84%)
occurrences (all)	5	4	58
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	3
Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	26 / 95 (27.37%)
occurrences (all)	1	2	32
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	22 / 95 (23.16%)
occurrences (all)	1	0	24
Secretion discharge			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Suprapubic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Temperature intolerance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Xerosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	2
Immune system disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Breast pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Scrotal pain			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Uterine pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Respiratory, thoracic and mediastinal disorders			
Aphonia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 9 (22.22%) 2	8 / 95 (8.42%) 9
Dysphonia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	4 / 95 (4.21%) 4
Dyspnoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 9 (22.22%) 2	16 / 95 (16.84%) 16
Dyspnoea at rest subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	4 / 95 (4.21%) 4
Haemoptysis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Increased upper airway secretion			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	0	0	3
Pharyngeal inflammation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Pleuritic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	1	0	3
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Sleep apnoea syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Bruxism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1

Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	2
Depression			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Mental status changes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	19 / 95 (20.00%)
occurrences (all)	0	2	32
Amylase increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	7 / 95 (7.37%)
occurrences (all)	1	4	13
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	38 / 95 (40.00%)
occurrences (all)	1	2	49
Bilirubin conjugated increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	15 / 95 (15.79%)
occurrences (all)	0	4	20
Blood bilirubin increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	6 / 95 (6.32%)
occurrences (all)	1	0	7
Blood creatine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 9 (33.33%)	37 / 95 (38.95%)
occurrences (all)	0	3	50
Blood creatinine decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	11 / 95 (11.58%)
occurrences (all)	2	0	16
Blood urea increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	4 / 95 (4.21%)
occurrences (all)	1	0	4
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	8 / 95 (8.42%)
occurrences (all)	0	1	9
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Lipase increased			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 9 (22.22%) 4	9 / 95 (9.47%) 17
Liver function test increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	4 / 95 (4.21%) 4
Monocyte count decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	10 / 95 (10.53%) 15
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	10 / 95 (10.53%) 11
Weight decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 9 (22.22%) 2	7 / 95 (7.37%) 7
Weight increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	9 / 95 (9.47%) 13
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Avulsion fracture			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Fracture subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Thermal burn subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Wrist fracture subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Cardiac disorders			
Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	1 / 95 (1.05%) 1
Mitral valve thickening subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 3
Ventricular arrhythmia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Nervous system disorders			
Ataxia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Balance disorder			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	11 / 95 (11.58%)
occurrences (all)	1	0	13
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	7 / 95 (7.37%)
occurrences (all)	0	1	9
Headache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	5 / 95 (5.26%)
occurrences (all)	1	0	6
Hyperaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	2
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	4
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	4 / 95 (4.21%)
occurrences (all)	0	0	6
Paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	0	0	4
Seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Taste disorder			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 2
Tongue paralysis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Transient ischaemic attack subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4	2 / 9 (22.22%) 3	40 / 95 (42.11%) 52
Leukopenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3	0 / 9 (0.00%) 0	5 / 95 (5.26%) 7
Lymphopenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Neutropenia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 9 (11.11%) 1	14 / 95 (14.74%) 21
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 9 (22.22%) 2	15 / 95 (15.79%) 20
Ear and labyrinth disorders			
Ear congestion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Tinnitus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Eye disorders			

Chorioretinopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	0	0	3
Eye irritation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Eye swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Periorbital oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Retinal detachment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Retinal disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Retinal exudates			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Subretinal fluid			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	0	0	3
Visual impairment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2

Vitreous floaters subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	3 / 95 (3.16%) 4
Abdominal distension subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Abdominal pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	2 / 9 (22.22%) 2	13 / 95 (13.68%) 15
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	3 / 95 (3.16%) 3
Anal incontinence subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Ascites subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Constipation subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	2 / 9 (22.22%) 2	17 / 95 (17.89%) 18
Diarrhoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	5 / 9 (55.56%) 6	50 / 95 (52.63%) 72
Dry mouth			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	10 / 95 (10.53%)
occurrences (all)	0	0	11
Duodenal ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	4 / 95 (4.21%)
occurrences (all)	1	2	5
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	4 / 95 (4.21%)
occurrences (all)	0	1	4
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences (all)	0	1	1
Intra-abdominal haematoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Lip dry			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Lip pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Lip swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Mouth ulceration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Nausea			

subjects affected / exposed	4 / 10 (40.00%)	5 / 9 (55.56%)	44 / 95 (46.32%)
occurrences (all)	5	6	58
Oesophageal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Oesophagitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Oral discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Retching			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	33 / 95 (34.74%)
occurrences (all)	1	0	42
Tongue discolouration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Tooth loss			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Vomiting			

subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	6 / 9 (66.67%) 8	38 / 95 (40.00%) 55
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Hepatosplenomegaly			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	6 / 95 (6.32%)
occurrences (all)	0	0	7
Dermatitis acneiform			
subjects affected / exposed	2 / 10 (20.00%)	5 / 9 (55.56%)	28 / 95 (29.47%)
occurrences (all)	2	5	40
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	16 / 95 (16.84%)
occurrences (all)	1	1	16
Eczema asteatotic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	4 / 95 (4.21%)
occurrences (all)	0	1	4
Hyperhidrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	1	0	3
Ingrowing nail			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Pain of skin			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Photosensitivity reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	3 / 95 (3.16%)
occurrences (all)	1	0	3
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	11 / 95 (11.58%)
occurrences (all)	0	0	13
Rash			
subjects affected / exposed	5 / 10 (50.00%)	1 / 9 (11.11%)	45 / 95 (47.37%)
occurrences (all)	5	1	71
Rash macular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	3
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	6 / 95 (6.32%)
occurrences (all)	1	0	6
Rash pruritic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Skin burning sensation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	2
Skin fissures			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	4 / 95 (4.21%)
occurrences (all)	0	0	4
Skin necrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Chronic kidney disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 95 (2.11%)
occurrences (all)	0	1	2
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	4 / 95 (4.21%)
occurrences (all)	0	1	4
Hydronephrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Micturition urgency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	7 / 95 (7.37%)
occurrences (all)	1	0	8
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Arthritis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	6 / 95 (6.32%)
occurrences (all)	1	3	7
Flank pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Groin pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 95 (1.05%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Muscle swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Muscle tightness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	4 / 95 (4.21%)
occurrences (all)	0	0	4
Myositis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Neck pain			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Pain in extremity subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Infections and infestations			
Arthritis infective subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Bronchitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Catheter site cellulitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Cellulitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Erysipelas subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	1 / 95 (1.05%) 2
Eye infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Fungal infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Herpes simplex subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Localised infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	2 / 95 (2.11%) 2
Paronychia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1

Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Postoperative wound infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Pustule			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 95 (2.11%)
occurrences (all)	0	1	2
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Staphylococcal skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Tinea cruris			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	0	4
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	8 / 95 (8.42%)
occurrences (all)	1	1	8
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Metabolism and nutrition disorders			
Appetite disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Decreased appetite subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	4 / 9 (44.44%) 4	21 / 95 (22.11%) 22
Dehydration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 2	9 / 95 (9.47%) 11
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	6 / 95 (6.32%) 7
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	2 / 95 (2.11%) 3
Hyperphosphataemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 95 (1.05%) 1
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	23 / 95 (24.21%) 25
Hypocalcaemia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	5 / 95 (5.26%)
occurrences (all)	0	0	5
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	12 / 95 (12.63%)
occurrences (all)	0	3	13
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	11 / 95 (11.58%)
occurrences (all)	0	2	16
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	5 / 95 (5.26%)
occurrences (all)	0	1	7
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2016	The purpose of this amendment was to instruct female subjects to use highly effective methods of contraception for 4 months after their last dose of the drug. The original protocol erroneously indicated that only 30 days of post-drug contraception was necessary. The 4-month period was based on a washout period (5 half-lives) calculated using the longest individual half-life (523 hours) observed with trametinib.
03 January 2017	The purpose of this amendment was to revise the treatment schedule in order to improve the safety of trametinib and ribociclib given in combination. DLTs were observed in the first 5 subjects of this study, along with other adverse events, which were already reported in prior single agent studies with either trametinib or ribociclib. The original 28-day cycle of continuous trametinib 2 mg and 3 weeks on/1 week off of ribociclib 200 mg was then modified to an intermittent schedule for safety reasons. A 21-day schedule of 2 weeks on/1 week-off of trametinib and ribociclib was explored with two different dosing schedules: Schedule 1 (trametinib administered once daily from Day 1 to Day 14, and ribociclib administered once daily from Day 8 to Day 21 of a 21-day cycle. This schedule was assessed in successive cohorts of subjects receiving trametinib 1.5 to 2 mg and increasing doses of ribociclib (150 to 600 mg)); and Schedule 2: (trametinib administered once daily from Day 1 to Day 14, and ribociclib administered once daily from Day 1 to Day 14 of a 21-day cycle. This schedule was assessed with the MTD obtained with Schedule 1).
12 July 2018	This amendment was implemented in order to explore additional cohorts to achieve the target plasma concentrations for trametinib and establish MTD/RP2R. The following cohorts were explored in parallel: Cohort Xa (1.0 mg trametinib daily in combination with 300 mg ribociclib daily (using Schedule 1)); and Cohort Xb (1.0 mg trametinib daily in combination with 400 mg ribociclib daily (using Schedule 1)). Based on the analyses of above 2 cohorts, there was an option to assess additional cohorts (Ya and Yb) with 0.5 mg trametinib in combination with ribociclib, if 1 mg trametinib was not tolerated. The decision to test either Ya or Yb, or both cohorts in parallel was to be made based on BLRM, safety and PK data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Upon careful review of all available efficacy and safety data from the study phase Ib part, Novartis decided to not start the study phase II part. This decision was in no means triggered by an unfavorable safety profile of the combination.

Notes: