



Clinical trial results:

A Phase Ib/II, open label, multi-center study evaluating the safety and efficacy of BKM120 in combination with trastuzumab in patients with relapsing HER2 overexpressing breast cancer who have previously failed trastuzumab

Summary

EudraCT number	2009-015417-46
Trial protocol	GB BE
Global end of trial date	07 August 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	CBKM120X2107
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01132664
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	07 August 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Phase Ib was to determine the maximum-tolerated dose (MTD) of buparlisib when administered orally in combination with weekly trastuzumab to adult patients with HER2-overexpressing breast cancer that is resistant to trastuzumab therapy.

The phase II was to determine the activity of buparlisib in combination with weekly trastuzumab as measured by objective response rate (ORR) in patients with HER2-overexpressing breast cancer that is resistant to trastuzumab therapy.

This study was extended to include HER2 positive breast cancer patients with brain metastasis (to determine the MTD/RP2D, safety, tolerability and preliminary anti-tumor activity) of oral buparlisib and capecitabine in combination with fixed dose trastuzumab. However, the brain metastasis part was terminated after completion of the first three dose escalation cohorts due to recruitment challenges.

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	17 May 2010
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: 8
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	68
EEA total number of subjects	53

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)	60
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

72 patients (pts) were enrolled: 18 in ph Ib, 53 in ph II, including 8 from ph Ib, with 45 new pts in ph II & 9 in the brain metastasis (BM) cohort. Of the 72 pts, 1 in ph Ib & 3 in phase II, did not receive Burparlisib, only Trastuzumab. Therefore, 68 patients (17 in ph I, 42 in ph II, 9 in BM cohort) were treated with buparlisib + trastuzumab.

Pre-assignment

Screening details:

Primary outcome measure for BM cohort was MTD/RP2D which was not reached/established due to termination of the study.

Objective Response Rate (ORR), Disease Control Rate (DCR), Clinical Benefit Rate (CBR) & Progression Free Survival (PFS) were not calculated for the BM cohort either.

Period 1

Period 1 title	Overall (Phase I, Phase II, BM Cohort) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Phase Ib - 50 mg

Arm description:

Patients in the phase Ib dose escalation cohort who received 50 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently

Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Burparlisib was supplied as 10 mg and 50 mg hard gelatin capsules

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently

Arm title	Phase Ib - 100mg
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Arm description:

Patients in the phase Ib dose escalation cohort who received 100 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently

Arm type	Experimental
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Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Burparlisib was supplied as 10 mg and 50 mg hard gelatin capsules	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Arm title	Phase II - 100mg
Arm description:	
Patients in the phase II expansion + patients from phase Ib dose escalation were included in phase II and received 100 mg of investigational drug - buparlisib + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Burparlisib was supplied as 10 mg and 50 mg hard gelatin capsules	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Arm title	BM Cohort - 80mg
Arm description:	
Patients in the BM cohort who received 80 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently + capecitabine 1000 mg/m ² twice a day from Day 1 to Day 14 of a 21- day cycle.	
Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Burparlisib was supplied as 10 mg and 50 mg hard gelatin capsules	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:	
4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m² twice a day from Day 1 to Day 14 of a 21- day cycle

Arm title	BM Cohort - 100mg
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Arm description:

Patients in the BM cohort who received 100 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently + capecitabine 1000 mg/m² twice a day from Day 1 to Day 14 of a 21- day cycle.

Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Burparlisib was supplied as 10 mg and 50 mg hard gelatin capsules

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m² twice a day from Day 1 to Day 14 of a 21- day cycle

Number of subjects in period 1	Phase Ib - 50 mg	Phase Ib - 100mg	Phase II - 100mg
Started	5	12	42
Completed	0	0	0
Not completed	5	12	42
Adverse event, serious fatal	-	-	2
Consent withdrawn by subject	1	2	2
Adverse event, non-fatal	-	1	9
Disease Progression	4	9	29

Number of subjects in period 1	BM Cohort - 80mg	BM Cohort - 100mg
Started	3	6
Completed	0	0
Not completed	3	6
Adverse event, serious fatal	-	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1
Disease Progression	3	4

Baseline characteristics

Reporting groups

Reporting group title	Phase Ib - 50 mg
Reporting group description:	
Patients in the phase Ib dose escalation cohort who received 50 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Reporting group title	Phase Ib - 100mg
Reporting group description:	
Patients in the phase Ib dose escalation cohort who received 100 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Reporting group title	Phase II - 100mg
Reporting group description:	
Patients in the phase II expansion + patients from phase Ib dose escalation were included in phase II and received 100 mg of investigational drug - buparlisib + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Reporting group title	BM Cohort - 80mg
Reporting group description:	
Patients in the BM cohort who received 80 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently + capecitabine 1000 mg/m2 twice a day from Day 1 to Day 14 of a 21- day cycle.	
Reporting group title	BM Cohort - 100mg
Reporting group description:	
Patients in the BM cohort who received 100 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently + capecitabine 1000 mg/m2 twice a day from Day 1 to Day 14 of a 21- day cycle.	

Reporting group values	Phase Ib - 50 mg	Phase Ib - 100mg	Phase II - 100mg
Number of subjects	5	12	42
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	11	35
From 65-84 years	0	1	7
Gender, Male/Female			
Units: Participants			
Female	5	12	42
Male	0	0	0
Study Specific Characteristic			
Units: Subjects			
Able to bear children	2	3	8
Premenarche	0	0	0
Post-menopausal	3	8	31
Sterile - of child bearing age	0	1	3

Reporting group values	BM Cohort - 80mg	BM Cohort - 100mg	Total
Number of subjects	3	6	68
Age categorical			
Units: Subjects			
Adults (18-64 years)	3	6	60
From 65-84 years	0	0	8

Gender, Male/Female			
Units: Participants			
Female	3	6	68
Male	0	0	0
Study Specific Characteristic			
Units: Subjects			
Able to bear children	1	1	15
Premenarche	0	0	0
Post-menopausal	2	4	48
Sterile - of child bearing age	0	1	5

End points

End points reporting groups

Reporting group title	Phase Ib - 50 mg
Reporting group description: Patients in the phase Ib dose escalation cohort who received 50 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Reporting group title	Phase Ib - 100mg
Reporting group description: Patients in the phase Ib dose escalation cohort who received 100 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Reporting group title	Phase II - 100mg
Reporting group description: Patients in the phase II expansion + patients from phase Ib dose escalation were included in phase II and received 100 mg of investigational drug - buparlisib + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently	
Reporting group title	BM Cohort - 80mg
Reporting group description: Patients in the BM cohort who received 80 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently + capecitabine 1000 mg/m ² twice a day from Day 1 to Day 14 of a 21- day cycle.	
Reporting group title	BM Cohort - 100mg
Reporting group description: Patients in the BM cohort who received 100 mg of buparlisib - investigational drug + trastuzumab 4 mg/kg loading dose iv infusion (if required) on Day -7, 2 mg/kg weekly iv infusion subsequently + capecitabine 1000 mg/m ² twice a day from Day 1 to Day 14 of a 21- day cycle.	
Subject analysis set title	Phase II 100 mg 50 patients
Subject analysis set type	Full analysis
Subject analysis set description: phase II plus 8 patients from phase Ib	

Primary: Dose Limiting Toxicity (DLT) - Phase I only

End point title	Dose Limiting Toxicity (DLT) - Phase I only ^{[1][2]}
End point description: Determination of the maximum tolerated dose (MTD) in the dose escalation part of the study was based upon the estimation of the probability of DLT in Cycle 1 in patients of the dose-determining set. The Dose-determining set (DDS) for the determination of the MTD consisted of all patients from the safety set in the dose escalation phase who had met the minimum safety evaluation requirements and the minimum exposure criterion or had experienced DLT during Cycle 1 and were discontinued. MTD analysis was done only on the phase Ib group.	
End point type	Primary
End point timeframe: cycle 1 - 28 days	

Notes:

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

Justification: There was no planned analysis.

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

Justification: Only summary analysis are provided for this measure and EudraCT can only accept analysis that compares one arm versus another.

End point values	Phase Ib - 50 mg	Phase Ib - 100mg	BM Cohort - 80mg	BM Cohort - 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	3	5
Units: Participants				
Primary system organ class (SOC) PT - grade 1	0	0	0	0
Primary SOC PT - grade 2	0	0	0	0
Primary SOC PT (asthenia) - grade 3	0	1	0	0
Primary SOC PT - grade 4	0	0	0	0
Primary SOC PT - missing	0	0	0	0
Primary SOC PT (somatits/diarrhea) - grade 3	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) - Phase II

End point title	Overall Response Rate (ORR) - Phase II ^[3]
End point description:	
Objective response rate (ORR) was defined as the rate of patients with best overall response (BOR) equal to complete response (CR) or partial response (PR) according to RECIST 1.0 from the Investigators review. Per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 assessed of the disease status by imaging (i.e. CT/MRI): Complete Response (CR) = Disappearance of all tumor lesions; Partial Response (PR)= ≥30% shrinkage of lesions; Overall Response (OR) = patients with CR and PR. The full analysis set (FAS) consisted of all patients who received at least one dose of study drug (buparlisib)	
End point type	Primary
End point timeframe:	
18 months	
Notes:	
[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: There was no planned analysis.	

End point values	Phase II 100 mg 50 patients			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Participants	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) based on Investigator assessment- Phase I & II

End point title	Disease control rate (DCR) based on Investigator assessment-Phase I & II ^[4]
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End point description:

Disease control rate (DCR) = patients with complete response (CR), partial response (PR) or stable disease (SD) as per RECIST criteria. Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 assessed the disease status by imaging (i.e. CT/MRI): CR = disappearance of all tumor lesions; PR = $\geq 30\%$ shrinkage of lesions; SD = Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease (PD); PD = At least a 20% increase in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline. The full analysis set (FAS) consisted of all patients who received at least one dose of study drug (buparlisib).

End point type	Secondary
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End point timeframe:

18 months

Notes:

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

Justification: This endpoint was for only Phase I and II arms.

End point values	Phase Ib - 50 mg	Phase Ib - 100mg	Phase II 100 mg 50 patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	12	50	
Units: Participants				
Phase I	1	7	0	
Phase II	0	0	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR) - Phase I & II

End point title	Clinical benefit rate (CBR) - Phase I & II ^[5]
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End point description:

CBR = patients with CR, PR or SD ≥ 24 weeks according to RECIST by the investigator. Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 assessed the disease status by imaging (i.e. CT/MRI): CR = Disappearance of all tumor lesions; PR= $\geq 30\%$ shrinkage of lesions;SD = Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease (PD); PD = At least a 20% increase in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline. The full analysis set (FAS) consisted of all patients who received at least one dose of study drug (buparlisib).

End point type	Secondary
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End point timeframe:

18 months

Notes:

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

Justification: There was no planned analysis.

End point values	Phase Ib - 50 mg	Phase Ib - 100mg	Phase II 100 mg 50 patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	12	50	
Units: Participants				
Phase I	0	3	0	
Phase II	0	0	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) - based on investigator review using Kaplan Meier - Phase I

End point title	Progression free survival (PFS) - based on investigator review using Kaplan Meier - Phase I ^[6]
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End point description:

End point type	Secondary
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End point timeframe:

18 months

Notes:

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

Justification: This endpoint was only for Phase I arm.

End point values	Phase Ib - 50 mg	Phase Ib - 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	12		
Units: Months				
median (confidence interval 90%)	1.7 (1.3 to 3.6)	3.3 (1.6 to 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) - based on investigator review using Kaplan Meier - Phase II

End point title	Progression free survival (PFS) - based on investigator review using Kaplan Meier - Phase II
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End point description:

PFS Was Analyzed Only in Patients With Known PIK3 Status, Thus Only 26/50 Patients Were Analyzed. The full analysis set (FAS) consisted of all patients who received at least one dose of study drug (buparlisib).

End point type	Secondary
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End point timeframe:

18 months

End point values	Phase II 100 mg 50 patients			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Months				
median (confidence interval 90%)				
Phase II: PIK3CA wildtype (n =18)	1.7 (1.5 to 5.4)			
Phase II: PIK3CA mutated (n =8)	1.8 (1.3 to 3.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

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	17.0
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Reporting groups

Reporting group title	Phase Ib Dose escalation 50 mg/day
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Reporting group description:

Phase Ib Dose escalation 50 mg/day

Reporting group title	Phase II Dose expansion 0 mg/day
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Reporting group description:

Phase II Dose expansion 0 mg/day

Reporting group title	Phase Ib Dose escalation 100 mg/day
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Reporting group description:

Phase Ib Dose escalation 100 mg/day

Reporting group title	BM cohort 80 mg/day
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Reporting group description:

BM cohort 80 mg/day

Reporting group title	All Phase Ib + II
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Reporting group description:

All Phase Ib + II

Reporting group title	BM cohort 100 mg/day
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Reporting group description:

BM cohort 100 mg/day

Reporting group title	Phase II Dose expansion 100 mg/day
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Reporting group description:

Phase II Dose expansion 100 mg/day

Serious adverse events	Phase Ib Dose escalation 50 mg/day	Phase II Dose expansion 0 mg/day	Phase Ib Dose escalation 100 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	1 / 3 (33.33%)	2 / 12 (16.67%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Hyperpyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	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
Oedema Peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (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
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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			
Acute Respiratory Failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	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
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Pleural Effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 Failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Psychiatric disorders			
Affective Disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Confusional State			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Delirium			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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

Depressed Mood			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Mood Altered			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Bilirubin Conjugated Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 Bilirubin Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Nervous system disorders			
Cerebral Haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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

Cerebrovascular Accident			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Convulsion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Epilepsy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Status Epilepticus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 / 3 (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
Lymphadenopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 Upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (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
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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

Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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			
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Hepatic Failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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			
Photosensitivity Reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 Maculo-Papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 and connective tissue disorders			
Bone Pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Muscular Weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 Stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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			
Device Related Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Lobar Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Lung Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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%)	0 / 3 (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			
Diabetic Ketoacidosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Hypercreatininaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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	BM cohort 80 mg/day	All Phase Ib + II	BM cohort 100 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	20 / 63 (31.75%)	4 / 6 (66.67%)
number of deaths (all causes)	0	5	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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 disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Hyperpyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Oedema Peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural Effusion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (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 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Psychiatric disorders			
Affective Disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Confusional State			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (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
Depressed Mood			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Depression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Mood Altered			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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 / 1	0 / 0
Bilirubin Conjugated Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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 / 1	0 / 0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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 / 1	0 / 0
Nervous system disorders			
Cerebral Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Cerebrovascular Accident			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Convulsion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (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 / 0	0 / 0	0 / 0

Epilepsy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Status Epilepticus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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

Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Hepatic Failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Skin and subcutaneous tissue disorders			
Photosensitivity Reaction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash Maculo-Papular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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			
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (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
Muscular Weakness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Musculoskeletal Stiffness			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Infections and infestations			
Device Related Infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Lobar Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (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 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (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
Lung Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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
Sepsis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (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 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Hypercreatininaemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (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
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	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

Serious adverse events	Phase II Dose expansion 100 mg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 50 (34.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General Physical Health Deterioration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperpyrexia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pneumonitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory Failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 0 / 1 0 / 0		
Psychiatric disorders Affective Disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 1 / 1 0 / 0		
Confusional State subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 1 / 1 0 / 0		
Delirium subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 50 (0.00%) 0 / 0 0 / 0		
Depressed Mood subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 1 / 1 0 / 0		
Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 1 / 1 0 / 0		
Mood Altered subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 1 / 1 0 / 0		
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 50 (4.00%) 1 / 2 0 / 1		

Aspartate Aminotransferase Increased				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Bilirubin Conjugated Increased				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blood Bilirubin Increased				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cerebral Haemorrhage				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular Accident				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Status Epilepticus				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Photosensitivity Reaction			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rash Maculo-Papular			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular Weakness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Stiffness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device Related Infection			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lobar Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercreatininaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase Ib Dose escalation 50 mg/day	Phase II Dose expansion 0 mg/day	Phase Ib Dose escalation 100 mg/day
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 5 (100.00%)	2 / 3 (66.67%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour Pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Vascular disorders Hot Flush subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Hypertension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	3 / 12 (25.00%) 4
Orthostatic Hypotension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 3 (0.00%) 0	6 / 12 (50.00%) 8
Chest Pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Chills subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Face Oedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0

Gait Disturbance subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Injection Site Reaction subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Mucosal Dryness subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	2 / 12 (16.67%) 3
Mucosal Inflammation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Non-Cardiac Chest Pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Oedema Peripheral subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Pyrexia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Reproductive system and breast disorders Breast Pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Vulvovaginal Discomfort subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	0	8
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Interstitial Lung Disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pleural Effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pleuritic Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Productive Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory Disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Affective Disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	6
Anxiety			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Binge Eating			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depressed Mood			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Initial Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Irritability			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mood Altered			
subjects affected / exposed	3 / 5 (60.00%)	0 / 3 (0.00%)	4 / 12 (33.33%)
occurrences (all)	3	0	4
Nervousness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Restlessness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Suicidal Ideation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Investigations			

Alanine Aminotransferase Decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1	4 / 12 (33.33%) 7
Amylase Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1	4 / 12 (33.33%) 9
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	2 / 12 (16.67%) 3
Blood Bilirubin Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 12 (0.00%) 0
Blood Calcium Decreased subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 3	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Blood Cholesterol Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Blood Creatine Phosphokinase Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 12 (0.00%) 0
Blood Creatine Phosphokinase Mb Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 12 (0.00%) 0
Blood Creatinine Increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1
Blood Glucose Decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood Glucose Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood Uric Acid Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
C-Reactive Protein Increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eastern Cooperative Oncology Group Performance Status Worsened			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ejection Fraction Decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Glycosylated Haemoglobin Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	3 / 12 (25.00%)
occurrences (all)	1	1	5
Haemoglobin Decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Insulin C-Peptide Increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lipase Increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Liver Function Test Abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Low Density Lipoprotein Increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lymphocyte Count Decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Protein Urine Present			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Weight Decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rib Fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Spinal Fracture			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tooth Fracture			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vaginal Laceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	4
Wound Complication			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Balance Disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cluster Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Memory Impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neuropathy Peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			

subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Extraocular Muscle Paresis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye Irritation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye Pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ocular Hyperaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vision Blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Visual Impairment			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	3
Abdominal Pain Lower			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Anal Fissure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aphthous Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	5 / 12 (41.67%)
occurrences (all)	2	0	35
Dry Mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	4
Haemorrhoids Thrombosed			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lip Ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mouth Ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Nausea			
subjects affected / exposed	2 / 5 (40.00%)	1 / 3 (33.33%)	3 / 12 (25.00%)
occurrences (all)	3	1	3
Pigmentation Lip			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	0	6
Tongue Discolouration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth Disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	3 / 12 (25.00%)
occurrences (all)	3	0	3
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dermatitis Acneiform			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Dry Skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	4
Eczema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nail Disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Night Sweats			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Photosensitivity Reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	5
Pruritus			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	5 / 12 (41.67%)
occurrences (all)	3	0	7
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	6 / 12 (50.00%)
occurrences (all)	1	0	8
Rash Generalised			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rash Maculo-Papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash Pruritic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin Discolouration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Skin Exfoliation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin Lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Swelling Face			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Micturition Urgency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (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 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Back Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Bone Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle Spasms			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscular Weakness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal Pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pain In Extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Device Related Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eczema Infected			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Furuncle			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Herpes Zoster			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Oral Herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	5 / 12 (41.67%)
occurrences (all)	2	0	8
Hyperphagia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	5
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Increased Appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	BM cohort 80 mg/day	All Phase Ib + II	BM cohort 100 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	61 / 63 (96.83%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypertension			

subjects affected / exposed	0 / 3 (0.00%)	6 / 63 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	7	0
Orthostatic Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	16 / 63 (25.40%)	1 / 6 (16.67%)
occurrences (all)	0	20	1
Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Face Oedema			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	3 / 3 (100.00%)	16 / 63 (25.40%)	4 / 6 (66.67%)
occurrences (all)	4	20	5
Gait Disturbance			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Injection Site Reaction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mucosal Dryness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Mucosal Inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Non-Cardiac Chest Pain			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	7 / 63 (11.11%) 8	0 / 6 (0.00%) 0
Oedema Peripheral subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	4 / 63 (6.35%) 6	0 / 6 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 63 (1.59%) 1	0 / 6 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	6 / 63 (9.52%) 7	1 / 6 (16.67%) 1
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 63 (1.59%) 1	0 / 6 (0.00%) 0
Reproductive system and breast disorders Breast Pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 63 (0.00%) 0	1 / 6 (16.67%) 2
Vulvovaginal Discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 63 (0.00%) 0	1 / 6 (16.67%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	16 / 63 (25.40%) 21	1 / 6 (16.67%) 1
Dyspnoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	6 / 63 (9.52%) 6	0 / 6 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 63 (3.17%) 3	0 / 6 (0.00%) 0
Hiccups subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 63 (1.59%) 1	0 / 6 (0.00%) 0
Interstitial Lung Disease			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Pain			
subjects affected / exposed	1 / 3 (33.33%)	4 / 63 (6.35%)	2 / 6 (33.33%)
occurrences (all)	1	4	2
Pleural Effusion			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Pleuritic Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Productive Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Respiratory Disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Affective Disorder			
subjects affected / exposed	0 / 3 (0.00%)	5 / 63 (7.94%)	0 / 6 (0.00%)
occurrences (all)	0	8	0
Anxiety			
subjects affected / exposed	1 / 3 (33.33%)	11 / 63 (17.46%)	2 / 6 (33.33%)
occurrences (all)	4	11	2
Binge Eating			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Depressed Mood			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Depression			
subjects affected / exposed	0 / 3 (0.00%)	10 / 63 (15.87%)	1 / 6 (16.67%)
occurrences (all)	0	11	1

Initial Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	9 / 63 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	9	0
Irritability			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Mood Altered			
subjects affected / exposed	0 / 3 (0.00%)	11 / 63 (17.46%)	1 / 6 (16.67%)
occurrences (all)	0	11	1
Nervousness			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Restlessness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Suicidal Ideation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Investigations			
Alanine Aminotransferase Decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 3 (0.00%)	20 / 63 (31.75%)	1 / 6 (16.67%)
occurrences (all)	0	25	1
Amylase Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 3 (0.00%)	19 / 63 (30.16%)	1 / 6 (16.67%)
occurrences (all)	0	26	1
Blood Alkaline Phosphatase Increased			

subjects affected / exposed	0 / 3 (0.00%)	9 / 63 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	10	0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 63 (6.35%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Blood Calcium Decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Blood Cholesterol Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Blood Creatine Phosphokinase Mb Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Blood Creatinine Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Blood Glucose Decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood Glucose Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood Uric Acid Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
C-Reactive Protein Increased			

subjects affected / exposed	1 / 3 (33.33%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Eastern Cooperative Oncology Group Performance Status Worsened			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Ejection Fraction Decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Glycosylated Haemoglobin Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 3 (0.00%)	10 / 63 (15.87%)	0 / 6 (0.00%)
occurrences (all)	0	12	0
Haemoglobin Decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Insulin C-Peptide Increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Lipase Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Liver Function Test Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Low Density Lipoprotein Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Protein Urine Present			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Weight Decreased			
subjects affected / exposed	1 / 3 (33.33%)	8 / 63 (12.70%)	1 / 6 (16.67%)
occurrences (all)	1	8	1
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Rib Fracture			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Spinal Fracture			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Tooth Fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vaginal Laceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Wound Complication			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			

Balance Disorder			
subjects affected / exposed	1 / 3 (33.33%)	5 / 63 (7.94%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Cluster Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	6 / 63 (9.52%)	1 / 6 (16.67%)
occurrences (all)	1	6	2
Dysgeusia			
subjects affected / exposed	1 / 3 (33.33%)	8 / 63 (12.70%)	1 / 6 (16.67%)
occurrences (all)	1	8	1
Headache			
subjects affected / exposed	1 / 3 (33.33%)	12 / 63 (19.05%)	2 / 6 (33.33%)
occurrences (all)	3	12	2
Memory Impairment			
subjects affected / exposed	1 / 3 (33.33%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Neuropathy Peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 63 (7.94%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	4 / 63 (6.35%)	1 / 6 (16.67%)
occurrences (all)	1	4	1

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	6 / 63 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Neutropenia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 3 (33.33%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Extraocular Muscle Paresis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye Irritation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ocular Hyperaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Photophobia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vision Blurred			
subjects affected / exposed	2 / 3 (66.67%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Visual Impairment			
subjects affected / exposed	1 / 3 (33.33%)	2 / 63 (3.17%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Gastrointestinal disorders			

Abdominal Distension			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Abdominal Pain			
subjects affected / exposed	0 / 3 (0.00%)	7 / 63 (11.11%)	1 / 6 (16.67%)
occurrences (all)	0	12	1
Abdominal Pain Lower			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abdominal Pain Upper			
subjects affected / exposed	1 / 3 (33.33%)	6 / 63 (9.52%)	1 / 6 (16.67%)
occurrences (all)	2	7	1
Anal Fissure			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Aphthous Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Cheilitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	7 / 63 (11.11%)	2 / 6 (33.33%)
occurrences (all)	1	9	2
Diarrhoea			
subjects affected / exposed	3 / 3 (100.00%)	29 / 63 (46.03%)	5 / 6 (83.33%)
occurrences (all)	8	83	12
Dry Mouth			
subjects affected / exposed	1 / 3 (33.33%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Dyspepsia			
subjects affected / exposed	3 / 3 (100.00%)	8 / 63 (12.70%)	0 / 6 (0.00%)
occurrences (all)	3	8	0
Dysphagia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	3	0

Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Haematochezia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Haemorrhoids Thrombosed			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lip Ulceration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mouth Ulceration			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	29 / 63 (46.03%)	4 / 6 (66.67%)
occurrences (all)	3	53	8
Pigmentation Lip			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 3 (33.33%)	12 / 63 (19.05%)	2 / 6 (33.33%)
occurrences (all)	1	22	2
Tongue Discolouration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tooth Disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Toothache			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	16 / 63 (25.40%)	4 / 6 (66.67%)
occurrences (all)	2	26	11
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dermatitis Acneiform			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Dry Skin			
subjects affected / exposed	1 / 3 (33.33%)	7 / 63 (11.11%)	0 / 6 (0.00%)
occurrences (all)	1	8	0
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Nail Disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Night Sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	1 / 3 (33.33%)	2 / 63 (3.17%)	3 / 6 (50.00%)
occurrences (all)	1	2	5
Photosensitivity Reaction			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Pruritus			
subjects affected / exposed	3 / 3 (100.00%)	12 / 63 (19.05%)	0 / 6 (0.00%)
occurrences (all)	3	23	0
Rash			
subjects affected / exposed	2 / 3 (66.67%)	19 / 63 (30.16%)	1 / 6 (16.67%)
occurrences (all)	2	38	2
Rash Generalised			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash Maculo-Papular			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Rash Pruritic			
subjects affected / exposed	0 / 3 (0.00%)	4 / 63 (6.35%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Skin Discolouration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin Exfoliation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin Lesion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Swelling Face			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	1	1

Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Micturition Urgency			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Back Pain			
subjects affected / exposed	0 / 3 (0.00%)	7 / 63 (11.11%)	2 / 6 (33.33%)
occurrences (all)	0	9	2
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Muscle Spasms			
subjects affected / exposed	2 / 3 (66.67%)	5 / 63 (7.94%)	2 / 6 (33.33%)
occurrences (all)	3	11	2
Muscular Weakness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal Pain			
subjects affected / exposed	1 / 3 (33.33%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain In Extremity			
subjects affected / exposed	0 / 3 (0.00%)	5 / 63 (7.94%)	1 / 6 (16.67%)
occurrences (all)	0	7	2
Infections and infestations			

Cellulitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Cystitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Device Related Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear Infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Eczema Infected			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Herpes Zoster			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Oral Herpes			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	4	0

Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 63 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 3 (66.67%)	19 / 63 (30.16%)	4 / 6 (66.67%)
occurrences (all)	3	21	4
Hypercholesterolaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	19 / 63 (30.16%)	1 / 6 (16.67%)
occurrences (all)	1	24	1
Hyperphagia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 63 (3.17%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 63 (4.76%)	1 / 6 (16.67%)
occurrences (all)	2	5	3
Hyponatraemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 63 (1.59%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 63 (4.76%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Increased Appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 63 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Phase II Dose expansion 100 mg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	7		
Orthostatic Hypotension			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	16		
Chest Pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Chills			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	4		
Face Oedema			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	20		
Gait Disturbance			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Injection Site Reaction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Mucosal Dryness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
Mucosal Inflammation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Non-Cardiac Chest Pain			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	8		
Oedema Peripheral			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

Reproductive system and breast disorders			
Breast Pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Vulvovaginal Discomfort			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	19		
Dyspnoea			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Epistaxis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Interstitial Lung Disease			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Pleural Effusion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
Pleuritic Pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Productive Cough			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Respiratory Disorder			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Affective Disorder			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	8		
Anxiety			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	11		
Binge Eating			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Delirium			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Depressed Mood			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	9		
Initial Insomnia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Irritability			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Mood Altered			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Nervousness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		

Restlessness			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Suicidal Ideation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine Aminotransferase Decreased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Alanine Aminotransferase Increased			
subjects affected / exposed	18 / 50 (36.00%)		
occurrences (all)	23		
Amylase Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Aspartate Aminotransferase Increased			
subjects affected / exposed	17 / 50 (34.00%)		
occurrences (all)	24		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	9		
Blood Bilirubin Increased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
Blood Calcium Decreased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Blood Cholesterol Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	3		
Blood Creatine Phosphokinase Mb			

Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood Creatinine Increased			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Blood Glucose Decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood Glucose Increased			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Blood Uric Acid Increased			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
C-Reactive Protein Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eastern Cooperative Oncology Group Performance Status Worsened			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Ejection Fraction Decreased			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Glycosylated Haemoglobin Increased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	10		
Haemoglobin Decreased			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Insulin C-Peptide Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Lipase Increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Liver Function Test Abnormal			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Low Density Lipoprotein Increased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Protein Urine Present			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Weight Decreased			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Rib Fracture			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Spinal Fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Tooth Fracture			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Vaginal Laceration			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Wound Complication			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Nervous system disorders			
Balance Disorder			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Cluster Headache			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Dysgeusia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	11		
Memory Impairment			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Neuropathy Peripheral			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Eye disorders			
Dry Eye			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Extraocular Muscle Paresis			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye Irritation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Eye Pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Ocular Hyperaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vision Blurred			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Visual Impairment			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Abdominal Pain			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	12		
Abdominal Pain Lower			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Abdominal Pain Upper			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Anal Fissure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		

Aphthous Stomatitis			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
Cheilitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	25 / 50 (50.00%)		
occurrences (all)	77		
Dry Mouth			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Dysphagia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Haematochezia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Haemorrhoids Thrombosed			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		

Lip Ulceration			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Mouth Ulceration			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	26 / 50 (52.00%)		
occurrences (all)	49		
Pigmentation Lip			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	22		
Tongue Discolouration			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Tooth Disorder			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	14 / 50 (28.00%)		
occurrences (all)	23		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Dermatitis Acneiform			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Dry Skin			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Eczema			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	6		
Erythema			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
Nail Disorder			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Night Sweats			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Photosensitivity Reaction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	19		
Rash			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	35		
Rash Generalised			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Rash Maculo-Papular			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		

Rash Pruritic subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Skin Discolouration subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Skin Exfoliation subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Skin Lesion subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Swelling Face subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Renal and urinary disorders Chromaturia subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Dysuria subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Haematuria subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Micturition Urgency subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Back Pain subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 8		
Bone Pain			

subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Muscle Spasms			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	10		
Muscular Weakness			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Musculoskeletal Pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Pain In Extremity			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	7		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Device Related Sepsis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Ear Infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		

Eczema Infected			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Herpes Zoster			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Oral Herpes			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Paronychia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	4		
Pharyngitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Urinary Tract Infection			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	18 / 50 (36.00%)		
occurrences (all)	19		
Hypercholesterolaemia			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	18		
Hyperphagia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Hypoglycaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
Increased Appetite			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2010	<ul style="list-style-type: none">• Removed references to consenting and collecting follow-up data on partners of male patients who become pregnant while the male patient was receiving treatment with buparlisib and Trastuzumab.• Clarified the dose modification requirements around mood disorders particularly as it related to total score on the PHQ-9 assessment and response to question number 9 regarding suicidality.
15 January 2011	<ul style="list-style-type: none">• Greater specificity was provided concerning patient inclusion criteria with respect to prior chemotherapy and prior biological therapy received.• The pre-screening and analysis in the Phase II part of the study according to PIK3CA status (mutants vs. wild-type) was no longer required• Some of the secondary objectives and endpoints associated with biomarker assessments were changed to exploratory objectives and endpoints• The response rate thresholds for futility (15%) and activity (25%) were modified based on the population change in the Phase II setting (PIK3CA mutants and wild type patients were evaluated together in the same expansion cohort), and to be clinically relevant• The changes to inclusion/exclusion criteria, dose reduction guidelines, toxicity management guidelines were made to enhance the safety of enrolled patients• New preclinical data revealed the genotoxic potential of buparlisib, and the language regarding the contraception requirements and pregnancy follow up was revised• The minimum required number of 12 paired (6 per arm) pre- and post-buparlisib treatment fresh biopsies, although still strongly recommended, was changed to only occur if feasible
13 August 2012	<ul style="list-style-type: none">• Objectives and study design for BM cohorts were updated• Additional inclusion and exclusion criteria, and treatment specified for patients in the BM cohorts were added• Data analysis plan for BM cohorts and statistical model for dose escalation in the BM cohorts was added• CBR was added as a secondary efficacy endpoint for the Phase Ib and Phase II parts• Pregnancy testing was required at Baseline and EOT for all women, regardless of childbearing potential• Dose modification guidelines were updated for hyperglycemia, LVEF change, skin toxicity and diarrhea based on additional clinical experience gained from studies of buparlisib• The FAS definition was clarified and now comprised patients who received at least one dose of buparlisib treatment• The cut-off score of PHQ-9 at the Screening visit was increased from 10 to 12 to be consistent with the evolving clinical experience of buparlisib in patients with cancer, and overruling of the cut-off score of PHQ-9 or GAD-7 by a psychiatric assessment at the Screening visit was removed

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.

The BM cohort was to include a Phase Ib dose escalation part and safety expansion part, however, the study was terminated during the dose escalation part due to the rare patient population and challenges to enroll patients.

Notes: