



Clinical trial results:

An open-label, randomized, multi-center, Phase III study to compare the safety and efficacy of TKI258 versus sorafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies

Summary

EudraCT number	2009-015459-25
Trial protocol	CZ NL BE ES HU SK IT DE SE AT GR GB NO
Global end of trial date	30 June 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	CTKI258A2302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01223027
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Director, Novartis Pharma AG, 41 613241111,
Scientific contact	Study Director, Novartis Pharma AG, 41 613241111, trialandresults.registry@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare dovitinib vs. sorafenib with respect to progression free survival (PFS) determined by central radiology assessment in patients with mRCC after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies.

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	01 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 60
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 24
Country: Number of subjects enrolled	Netherlands: 11

Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 65
Worldwide total number of subjects	570
EEA total number of subjects	328

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)	352
From 65 to 84 years	217
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening/Baseline assessments were performed within 28 days prior to the first dose of study treatment. Certain specified assessments were to be performed \leq 14 days prior to the start of the study treatment.

Period 1

Period 1 title	End of Treatment phase before F/u visits (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dovitinib + best supportive care (BSC)

Arm description:

Patients randomized to the dovitinib treatment arm received 500 mg of dovitinib taken orally on 5 days on/2 days off dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Dovitinib
Investigational medicinal product code	TKI258
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg capsule to deliver 500 mg 5 days on 2 days off regimen

Arm title	Sorafenib + BSC
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Arm description:

Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily.

Arm type	Active comparator
Investigational medicinal product name	tosylate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily.

Number of subjects in period 1	Dovitinib + best supportive care (BSC)	Sorafenib + BSC
	Started	284
Completed	35	40
Not completed	249	246
Adverse event, serious fatal	18	20
Physician decision	7	9
Adverse event, non-fatal	42	28
Progressive Disease	160	173
Lost to follow-up	1	1
Protocol deviation	2	-
Subject/guardian decision	19	15

Baseline characteristics

Reporting groups

Reporting group title	Dovitinib + best supportive care (BSC)
Reporting group description: Patients randomized to the dovitinib treatment arm received 500 mg of dovitinib taken orally on 5 days on/2 days off dosing schedule.	
Reporting group title	Sorafenib + BSC
Reporting group description: Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily.	

Reporting group values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC	Total
Number of subjects	284	286	570
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	187	165	352
From 65-84 years	96	121	217
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	60.6	61.1	-
standard deviation	± 10.39	± 10.09	-
Gender, Male/Female Units: Participants			
Female	71	67	138
Male	213	219	432
Age, Customized Units: Subjects			
< 65	187	165	352
≥ 65	97	121	218
Race/Ethnicity, Customized Units: Subjects			
Caucasian	233	232	465
Asian	42	40	82
Black	3	5	8
Unknown	1	6	7
Other	5	3	8
Study Specific Characteristic Units: Subjects			

100 - Normal no complaints; no evidence of disease	83	73	156
90 - Able to carry on normal activity	93	101	194
80 - Normal activity with efforts	73	83	156
70 - Cares for self	35	29	64
Study Specific Characteristic			
<p>Pts were place into 3 distinct risk groups based on the number of risk factors that the patient had at baseline: Low Karnofsky Performance Status: <80%, Low serum hemoglobin: males (≤ 13 g/dL); females (≤ 11.5 g/dL), High corrected serum calcium: ≥ 10 mg/dL. Pts in the favorable group are expected to live longer while patients in the poor risk group are expected to die sooner than the patients in the other groups. Favorable = Pt. had none of the risks; Intermediate = Patient had 1 risk factor; Poor = Pt. had 2 or 3 risk factors Missing = not enough information at baseline to categorize</p>			
Units: Subjects			
Favorable	70	65	135
Intermediate	156	155	311
Poor	54	61	115
Missing	4	5	9
Study Specific Characteristic			
Units: years			
arithmetic mean	74.9	75.5	
standard deviation	± 15.39	± 15.96	-

End points

End points reporting groups

Reporting group title	Dovitinib + best supportive care (BSC)
Reporting group description: Patients randomized to the dovitinib treatment arm received 500 mg of dovitinib taken orally on 5 days on/2 days off dosing schedule.	
Reporting group title	Sorafenib + BSC
Reporting group description: Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily.	

Primary: Progression Free Survival (PFS) per independent central radiology review

End point title	Progression Free Survival (PFS) per independent central radiology review
End point description: Assessed according to RECIST 1.1. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. If a patient had not progressed or died, on the date of the analysis cut-off or when he/she received any further anti-neoplastic therapy, PFS was censored on the date of last tumor assessment before the cutoff date or the anti-neoplastic therapy date. The distribution of PFS was estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals was presented by treatment group.	
End point type	Primary
End point timeframe: Until disease progression or discontinuation of treatment due to unacceptable toxicity	

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Participants				
median (confidence interval 95%)	3.7 (3.5 to 3.9)	3.6 (3.5 to 3.7)		

Statistical analyses

Statistical analysis title	PFS per independent central radiological review
Statistical analysis description: The primary statistical analysis to compare PFS between the two treatment arms was performed using a log-rank test stratified by MSKCC group.	
Comparison groups	Dovitinib + best supportive care (BSC) v Sorafenib + BSC

Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.063 [1]
Method	Logrank

Notes:

[1] - P-value is one tailed and is based on the stratified log rank test.

Secondary: Overall Survival (OS)

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

Overall survival (OS) was the key secondary endpoint and was defined as the time from date of randomization to the date of death due to any cause. If a patient was not known to have died, survival was censored on the date of last contact.

End point type	Secondary
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End point timeframe:

until at least 386 deaths are documented in the clinical database.

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Participants				
median (confidence interval)	11.1 (9.5 to 13.4)	11 (8.6 to 13.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Investigator's radiology review

End point title	Progression Free Survival (PFS) per Investigator's radiology review
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End point description:

PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. The primary analysis for PFS (based on central review) was also to be repeated on FAS considering the Investigator assessments and using the same analytical conventions as the primary analysis.

End point type	Secondary
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End point timeframe:

Until disease progression or discontinuation of treatment due to unacceptable toxicity

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Participants				
median (confidence interval 95%)	3.9 (3.7 to 5.1)	3.9 (3.7 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) by central radiology review

End point title	Overall response rate (ORR) by central radiology review
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End point description:

Overall response rate (ORR) was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR). Best overall response (BOR) for each patient was determined from the sequence of overall (lesion) responses according to the following rules: CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required. CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required. SD = at least one SD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR). PD = progression ≤ 17 weeks after randomization (and not qualifying for CR, PR or SD).

End point type	Secondary
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End point timeframe:

Until disease progression or discontinuation of treatment due to unacceptable toxicity

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Participants	11	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive worsening of Karnofsky performance status (KPS)

End point title	Time to definitive worsening of Karnofsky performance status (KPS)
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End point description:

Time to definitive worsening of Karnofsky performance status (KPS) was defined as the time from date of randomization to the date of definitive worsening of KPS or to the date of death whichever occurred earlier. Definitive worsening was defined as a definitive decrease in performance status by at least one Karnofsky category (i.e. at least 10 points less) compared to Baseline. Worsening was considered definitive if no later increase above the defined threshold was observed within the course of the study. A single measure reporting a decrease in Karnofsky performance status was sufficient to consider it as

definitive only if it was the last one available for this patient. Time to definitive worsening of KPS was analyzed at the time of the final analysis for PFS.

End point type	Secondary
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End point timeframe:

from date of randomization to the date of definitive worsening of KPS or to the date of death whichever occurred earlier

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Participants				
median (confidence interval 95%)	5.1 (3.8 to 6.5)	5.7 (4.6 to 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs): Time to deterioration of FKSI-DRS by at least 2 scores

End point title	Patient-reported outcomes (PROs): Time to deterioration of FKSI-DRS by at least 2 scores
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End point description:

The primary analyses of patient-reported outcomes was the Disease- Related Symptoms of the FKSI (FKSI-DRS). The compliance to the schedule of administration of both questionnaires, FKSI-DRS and EORTC QoLQ-C30, were summarized by treatment arm for each visit, as well as the number of patients who completed or not the QoL data. The statistical analysis was comprised of the estimation of the treatment difference in terms of the time to definitive deterioration of the FKSI-DRS from Baseline by at least 2 score units in patients with a maximum score at Baseline of 34. Time to definitive worsening was calculated from the date of randomization.

End point type	Secondary
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End point timeframe:

from date of randomization, at least 2 score units

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Months				
median (confidence interval 95%)	4.9 (4.5 to 6.6)	6.4 (5.5 to 7.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs): Time to definitive deterioration of the Physical Functioning (PF) scale of EORTC QLQ-C30 by at least 10%

End point title	Patient-reported outcomes (PROs): Time to definitive deterioration of the Physical Functioning (PF) scale of EORTC QLQ-C30 by at least 10%
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End point description:

The key secondary endpoints of patient reported outcomes were the physical functioning (PF, 5 items) and the global health status/QoL scale (QoL) scores of the EORTC QoLQ-C30. The compliance to the schedule of administration of both questionnaires, FKSI-DRS and EORTC QoLQ-C30, were summarized by treatment arm for each visit, as well as the number of patients who completed or not the QoL data. The statistical analysis was comprised of the estimation of the treatment difference in terms of the time to definitive deterioration by 10% of the PF scale of the EORTC QoLQ-C30. Time to definitive worsening was calculated from the date of randomization.

End point type	Secondary
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End point timeframe:
from date of randomization

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Months				
median (confidence interval 95%)	3.8 (3.2 to 4.6)	5.6 (4.5 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs): Time to definitive deterioration of the quality of life (QoL) scale of EORTC QLQ-C30 by at least 10%

End point title	Patient-reported outcomes (PROs): Time to definitive deterioration of the quality of life (QoL) scale of EORTC QLQ-C30 by at least 10%
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End point description:

The key secondary endpoints of patient reported outcomes were the physical functioning (PF, 5 items) and the global health status/QoL scale (QoL) scores of the EORTC QoLQ-C30. The compliance to the schedule of administration of both questionnaires, FKSI-DRS and EORTC QoLQ-C30, were summarized by treatment arm for each visit, as well as the number of patients who completed or not the QoL data. The statistical analysis was comprised of the estimation of the treatment difference in terms of the time to definitive deterioration by 10% of the QoL scale of the EORTC QoLQ-C30. Time to definitive worsening was calculated from the date of randomization.

End point type	Secondary
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End point timeframe:
from date of randomization

End point values	Dovitinib + best supportive care (BSC)	Sorafenib + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	286		
Units: Months				
median (confidence interval 95%)	3.7 (2.8 to 4.6)	4.5 (3.7 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose concentration in plasma in Dovitinib

End point title	Pre-dose concentration in plasma in Dovitinib ^[2]
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End point description:

Pre-dose concentrations of dovitinib were summarized by visit using PAS. All concentration data was listed by patient and time point using FAS. Mean pre-dose concentrations along with standard deviation (SD) was plotted over time if appropriate.

End point type	Secondary
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End point timeframe:

Week 2 Day 5, Week 4 Day 5, Week 6 Day 5

Notes:

[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: Pharmacokinetics was reported only on the Dovitinib arm.

End point values	Dovitinib + best supportive care (BSC)			
Subject group type	Reporting group			
Number of subjects analysed	284			
Units: ng/ml				
median (standard error)				
Week 2 Day 5 (n: 205)	128.06 (± 92.571)			
Week 4 Day 5 (n: 202)	114.08 (± 77.884)			
Week 6 Day 5 (n: 170)	118.27 (± 84.246)			

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 reported in this record are from date of 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	Dovitinib
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Reporting group description:

Dovitinib

Reporting group title	Sorafenib
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Reporting group description:

Sorafenib

Serious adverse events	Dovitinib	Sorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	140 / 280 (50.00%)	123 / 284 (43.31%)	
number of deaths (all causes)	42	47	
number of deaths resulting from adverse events	7	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED NEOPLASM			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT PLEURAL EFFUSION			

subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
METASTASES TO BLADDER			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
METASTATIC PAIN			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOPLASM PROGRESSION			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
OESOPHAGEAL CARCINOMA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION MALIGNANT			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
TUMOUR PAIN			
subjects affected / exposed	3 / 280 (1.07%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM			

subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHLEBITIS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR FRAGILITY			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 280 (1.07%)	6 / 284 (2.11%)	
occurrences causally related to treatment / all	2 / 4	4 / 6	
deaths causally related to treatment / all	0 / 1	1 / 1	
DEATH			

subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0
DISEASE PROGRESSION		
subjects affected / exposed	0 / 280 (0.00%)	3 / 284 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 3
FATIGUE		
subjects affected / exposed	5 / 280 (1.79%)	5 / 284 (1.76%)
occurrences causally related to treatment / all	6 / 6	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
GENERAL PHYSICAL HEALTH DETERIORATION		
subjects affected / exposed	11 / 280 (3.93%)	17 / 284 (5.99%)
occurrences causally related to treatment / all	1 / 12	0 / 17
deaths causally related to treatment / all	0 / 10	0 / 15
GENERALISED OEDEMA		
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
MALAISE		
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
MULTI-ORGAN FAILURE		
subjects affected / exposed	3 / 280 (1.07%)	3 / 284 (1.06%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 3	0 / 3
NON-CARDIAC CHEST PAIN		
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
OEDEMA PERIPHERAL		

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	3 / 280 (1.07%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERFORMANCE STATUS DECREASED			
subjects affected / exposed	1 / 280 (0.36%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
PYREXIA			
subjects affected / exposed	8 / 280 (2.86%)	5 / 284 (1.76%)	
occurrences causally related to treatment / all	4 / 9	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
SERUM SICKNESS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
GENITAL HAEMORRHAGE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
ACUTE RESPIRATORY FAILURE		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
ALVEOLITIS		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
ATELECTASIS		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
BRONCHIAL OBSTRUCTION		
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
COUGH		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
DYSPNOEA		
subjects affected / exposed	15 / 280 (5.36%)	16 / 284 (5.63%)
occurrences causally related to treatment / all	4 / 16	1 / 16
deaths causally related to treatment / all	1 / 4	0 / 7
EPISTAXIS		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
HAEMOPTYSIS		

subjects affected / exposed	0 / 280 (0.00%)	3 / 284 (1.06%)
occurrences causally related to treatment / all	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
HYDROTHORAX		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
HYPOXIA		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
PLEURAL EFFUSION		
subjects affected / exposed	10 / 280 (3.57%)	11 / 284 (3.87%)
occurrences causally related to treatment / all	0 / 12	2 / 11
deaths causally related to treatment / all	0 / 3	1 / 1
PNEUMONIA ASPIRATION		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
PNEUMONITIS		
subjects affected / exposed	1 / 280 (0.36%)	2 / 284 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
PNEUMOTHORAX		
subjects affected / exposed	2 / 280 (0.71%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
PRODUCTIVE COUGH		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
PULMONARY EMBOLISM		

subjects affected / exposed	7 / 280 (2.50%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	4 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
RESPIRATORY ARREST			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	4 / 280 (1.43%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	1 / 2	0 / 3	
Psychiatric disorders			
APATHY			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COMPLETED SUICIDE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	4 / 280 (1.43%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
DELIRIUM			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

ALANINE AMINOTRANSFERASE INCREASED		
subjects affected / exposed	1 / 280 (0.36%)	2 / 284 (0.70%)
occurrences causally related to treatment / all	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
AMYLASE INCREASED		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED		
subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)
occurrences causally related to treatment / all	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
BLOOD ALKALINE PHOSPHATASE INCREASED		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
BLOOD CREATININE INCREASED		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
HAEMATOOCRIT DECREASED		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
LIPASE INCREASED		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
LIVER FUNCTION TEST ABNORMAL		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

OXYGEN SATURATION DECREASED			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TROPONIN INCREASED			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	2 / 280 (0.71%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CONTRAST MEDIA REACTION			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HUMERUS FRACTURE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

OVERDOSE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WRIST FRACTURE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ATRIAL FIBRILLATION			

subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC TAMPONADE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY OCCLUSION			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR DYSFUNCTION			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL NECROSIS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
TACHYCARDIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
APHASIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONVULSION			

subjects affected / exposed	2 / 280 (0.71%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIC UNCONSCIOUSNESS			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEURALGIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROLOGICAL DECOMPENSATION			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	2 / 280 (0.71%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SYNCOPE			
subjects affected / exposed	2 / 280 (0.71%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	7 / 280 (2.50%)	8 / 284 (2.82%)	
occurrences causally related to treatment / all	2 / 7	7 / 10	
deaths causally related to treatment / all	1 / 1	0 / 1	
LEUKOPENIA			

subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
DIPLOPIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	7 / 280 (2.50%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	3 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 280 (0.71%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	2 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL TENDERNESS			

subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL FISSURE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLONIC FISTULA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 280 (0.36%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	10 / 280 (3.57%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	9 / 11	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
DYSPEPSIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	3 / 280 (1.07%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAECAL INCONTINENCE			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC PERFORATION			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL MOTILITY DISORDER			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	2 / 280 (0.71%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
ILEUS PARALYTIC			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	3 / 280 (1.07%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL HAEMORRHAGE			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0
LARGE INTESTINE PERFORATION		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0
LOWER GASTROINTESTINAL HAEMORRHAGE		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
NAUSEA		
subjects affected / exposed	6 / 280 (2.14%)	3 / 284 (1.06%)
occurrences causally related to treatment / all	5 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
OBSTRUCTION GASTRIC		
subjects affected / exposed	0 / 280 (0.00%)	3 / 284 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
ODYNOPHAGIA		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
ORAL PAIN		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
PANCREATITIS		
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
PNEUMOPERITONEUM		

subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
RETROPERITONEAL HAEMATOMA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETROPERITONEAL HAEMORRHAGE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	1 / 280 (0.36%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
VOMITING			
subjects affected / exposed	8 / 280 (2.86%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	7 / 9	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	1 / 280 (0.36%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
JAUNDICE CHOLESTATIC			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC FOOT			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
PRURITUS GENERALISED			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH GENERALISED			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN LESION			

subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC EPIDERMAL NECROLYSIS			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
TOXIC SKIN ERUPTION			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
AZOTAEMIA			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	0 / 280 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLLAKIURIA			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 280 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE CHRONIC			

subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
URINARY BLADDER HAEMORRHAGE			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY INCONTINENCE			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPERCALCAEMIA OF MALIGNANCY			
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Musculoskeletal and connective tissue disorders			
AMYOTROPHY			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ARTHRALGIA			
subjects affected / exposed	2 / 280 (0.71%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	5 / 280 (1.79%)	7 / 284 (2.46%)	
occurrences causally related to treatment / all	1 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	

BONE PAIN			
subjects affected / exposed	2 / 280 (0.71%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
FLANK PAIN			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC DISORDER			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOPATHY			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECK PAIN			

subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	3 / 280 (1.07%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COLUMN STENOSIS			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ANAL ABSCESS			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONJUNCTIVITIS			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
EMPHYSEMATOUS CYSTITIS		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
GASTROENTERITIS		
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
INFECTIVE GLOSSITIS		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
LOBAR PNEUMONIA		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
LUNG INFECTION		
subjects affected / exposed	1 / 280 (0.36%)	1 / 284 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
MENINGITIS CRYPTOCOCCAL		
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
PNEUMONIA		
subjects affected / exposed	8 / 280 (2.86%)	8 / 284 (2.82%)
occurrences causally related to treatment / all	1 / 9	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 4
PYELONEPHRITIS ACUTE		

subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	7 / 280 (2.50%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SPINAL CORD INFECTION			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 280 (0.36%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	2 / 280 (0.71%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
DECREASED APPETITE			
subjects affected / exposed	2 / 280 (0.71%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	
DEHYDRATION			

subjects affected / exposed	6 / 280 (2.14%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	3 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	3 / 280 (1.07%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	2 / 280 (0.71%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	3 / 280 (1.07%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHAGIA			

subjects affected / exposed	2 / 280 (0.71%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HYPOPROTEINAEMIA			
subjects affected / exposed	1 / 280 (0.36%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LACTIC ACIDOSIS			
subjects affected / exposed	0 / 280 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	0 / 280 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dovitinib	Sorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	268 / 280 (95.71%)	272 / 284 (95.77%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	55 / 280 (19.64%)	78 / 284 (27.46%)	
occurrences (all)	63	93	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	64 / 280 (22.86%)	45 / 284 (15.85%)	
occurrences (all)	74	47	
FATIGUE			
subjects affected / exposed	113 / 280 (40.36%)	97 / 284 (34.15%)	
occurrences (all)	126	118	
NON-CARDIAC CHEST PAIN			

subjects affected / exposed occurrences (all)	22 / 280 (7.86%) 25	21 / 284 (7.39%) 23	
OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	26 / 280 (9.29%) 28	20 / 284 (7.04%) 21	
PAIN subjects affected / exposed occurrences (all)	8 / 280 (2.86%) 9	16 / 284 (5.63%) 18	
PYREXIA subjects affected / exposed occurrences (all)	40 / 280 (14.29%) 47	39 / 284 (13.73%) 54	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	52 / 280 (18.57%) 61	52 / 284 (18.31%) 60	
DYSPHONIA subjects affected / exposed occurrences (all)	22 / 280 (7.86%) 23	26 / 284 (9.15%) 26	
DYSPNOEA subjects affected / exposed occurrences (all)	54 / 280 (19.29%) 61	49 / 284 (17.25%) 57	
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all)	15 / 280 (5.36%) 15	21 / 284 (7.39%) 25	
Investigations BLOOD ALKALINE PHOSPHATASE INCREASED subjects affected / exposed occurrences (all)	25 / 280 (8.93%) 27	5 / 284 (1.76%) 5	
GAMMA-GLUTAMYLTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	27 / 280 (9.64%) 30	8 / 284 (2.82%) 8	
LIPASE INCREASED subjects affected / exposed occurrences (all)	17 / 280 (6.07%) 20	11 / 284 (3.87%) 13	

WEIGHT DECREASED subjects affected / exposed occurrences (all)	63 / 280 (22.50%) 73	89 / 284 (31.34%) 92	
Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all)	27 / 280 (9.64%) 33	8 / 284 (2.82%) 8	
DYSGEUSIA subjects affected / exposed occurrences (all)	31 / 280 (11.07%) 31	9 / 284 (3.17%) 10	
HEADACHE subjects affected / exposed occurrences (all)	26 / 280 (9.29%) 32	25 / 284 (8.80%) 32	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	29 / 280 (10.36%) 33	30 / 284 (10.56%) 36	
Eye disorders LACRIMATION INCREASED subjects affected / exposed occurrences (all)	19 / 280 (6.79%) 19	3 / 284 (1.06%) 4	
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all)	34 / 280 (12.14%) 40	41 / 284 (14.44%) 47	
ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	28 / 280 (10.00%) 32	23 / 284 (8.10%) 24	
CONSTIPATION subjects affected / exposed occurrences (all)	50 / 280 (17.86%) 66	70 / 284 (24.65%) 77	
DIARRHOEA subjects affected / exposed occurrences (all)	185 / 280 (66.07%) 305	132 / 284 (46.48%) 200	
DRY MOUTH subjects affected / exposed occurrences (all)	23 / 280 (8.21%) 26	13 / 284 (4.58%) 16	

DYSPEPSIA			
subjects affected / exposed	32 / 280 (11.43%)	14 / 284 (4.93%)	
occurrences (all)	34	15	
NAUSEA			
subjects affected / exposed	146 / 280 (52.14%)	82 / 284 (28.87%)	
occurrences (all)	207	96	
STOMATITIS			
subjects affected / exposed	30 / 280 (10.71%)	55 / 284 (19.37%)	
occurrences (all)	35	60	
VOMITING			
subjects affected / exposed	122 / 280 (43.57%)	47 / 284 (16.55%)	
occurrences (all)	227	60	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	2 / 280 (0.71%)	61 / 284 (21.48%)	
occurrences (all)	2	62	
DERMATITIS ACNEIFORM			
subjects affected / exposed	23 / 280 (8.21%)	6 / 284 (2.11%)	
occurrences (all)	28	6	
DRY SKIN			
subjects affected / exposed	22 / 280 (7.86%)	26 / 284 (9.15%)	
occurrences (all)	25	27	
ERYTHEMA			
subjects affected / exposed	1 / 280 (0.36%)	15 / 284 (5.28%)	
occurrences (all)	1	22	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	32 / 280 (11.43%)	117 / 284 (41.20%)	
occurrences (all)	36	142	
PRURITUS			
subjects affected / exposed	15 / 280 (5.36%)	30 / 284 (10.56%)	
occurrences (all)	18	33	
RASH			
subjects affected / exposed	54 / 280 (19.29%)	48 / 284 (16.90%)	
occurrences (all)	65	62	
Endocrine disorders			

HYPOTHYROIDISM			
subjects affected / exposed	14 / 280 (5.00%)	10 / 284 (3.52%)	
occurrences (all)	14	10	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	27 / 280 (9.64%)	30 / 284 (10.56%)	
occurrences (all)	29	38	
BACK PAIN			
subjects affected / exposed	38 / 280 (13.57%)	33 / 284 (11.62%)	
occurrences (all)	43	37	
MUSCLE SPASMS			
subjects affected / exposed	19 / 280 (6.79%)	25 / 284 (8.80%)	
occurrences (all)	21	26	
MUSCULAR WEAKNESS			
subjects affected / exposed	14 / 280 (5.00%)	6 / 284 (2.11%)	
occurrences (all)	15	6	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	16 / 280 (5.71%)	14 / 284 (4.93%)	
occurrences (all)	16	14	
MYALGIA			
subjects affected / exposed	27 / 280 (9.64%)	17 / 284 (5.99%)	
occurrences (all)	33	17	
PAIN IN EXTREMITY			
subjects affected / exposed	36 / 280 (12.86%)	33 / 284 (11.62%)	
occurrences (all)	43	48	
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	16 / 280 (5.71%)	2 / 284 (0.70%)	
occurrences (all)	18	2	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	91 / 280 (32.50%)	98 / 284 (34.51%)	
occurrences (all)	111	109	
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	55 / 280 (19.64%)	2 / 284 (0.70%)	
occurrences (all)	64	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2010	Following an Investigator notification dated 16-Jul-2010 about a serious, unexpected, possibly study drug related adverse event of hepatotoxicity (cholestatic liver injury) in a patient and subsequent death of that patient enrolled into the CTKI258A2202 study, the protocol was amended to monitor liver function more closely and to allow early detection of study drug induced liver injury, if any. Gamma-glutamyl transferase (GGT) was added in order to have a complete liver function test.
09 February 2011	Change of inclusion criteria to require Baseline ALT, AST and total bilirubin grade 1 or less regardless of whether hepatic metastases are present at Baseline. Change of exclusion criteria to employ two forms of highly effective contraception for patients participating in the study, and for patients with partners who are biologically able to conceive based on an oral embryo-fetal development study in rats, showing that dovitinib is teratogenic. Addition of precautionary advice to avoid concomitant medication known to cause liver toxicity, as well as addition of list of hepatotoxic agents not permitted as concomitant medication in order to further reduce hepatotoxic events. Collection of a trough concentration at Day 5 Week 6 to obtain at least one dovitinib trough concentration at time points beyond Cycle 1 in order to have steady state PK to evaluate the potential relationship of safety and efficacy in regards to steady state.
01 September 2011	Novartis Oncology implemented a new radiology data review procedure in Phase III trials involving tumor assessments performed by the Investigator at the time of declaration of disease progression to decrease the rates of discordance between local and central interpretation of radiological data. At this precise time, an expedited tumor response evaluation by the central radiologist is required. The time to definitive worsening of KPS was added as a secondary objective. Patient stratification by 4 pre-determined geographic regions (Japan, Asia Pacific, Europe/Middle East and Americas) was added to document plans for an anticipated exploratory subgroup analysis of PFS based on geographic region.
25 January 2012	Based on the results of the food effect test (CTKI258A2112 Arm 2; FMI capsule formulation), dovitinib could be taken, as previously, without food, or with an amount of food up to the level tested, i.e. low-fat meal of \leq 500 calories with \leq 20 grams fat.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported