Clinical trial results:
Evaluation of the efficacy of high throughput genome analysis as a therapeutic decision tool for patients with metastatic non small cell lung cancer.

Summary

EudraCT number	2013-001653-27
Trial protocol	FR
Global end of trial date	31 December 2023

Results information

Result version number	v1 (current)
This version publication date	12 June 2025
First version publication date	12 June 2025

Trial information

Trial identification

Sponsor protocol code	UC_0105-1305_/_IFCT_1301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02117167
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75015
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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	12 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2020
Global end of trial reached?	Yes
Global end of trial date	31 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safir 02 Lung was an open-label multicentric randomized phase II trial, using high throughput genome analysis as a therapeutic decision tool, aimed at comparing a targeted treatment administered according to identified molecular anomalies of the tumor with a standard maintenance as per guidelines (targeted substudy 1: Arm A1 and B1) as well as immunotherapy versus maintenance therapy in patients without actionable genomic alterations or non eligible to substudy 1 (immune substudy 2: Arm A2 and B2).

The main objective was to evaluate whether treatment with targeted agents guided by high throughput molecular analyses (CGH array, next generation sequencing) improves overall progression-free survival as compared to standard maintenance therapy in patients with metastatic NSCLC ((primary objective of substudy 1).

Protection of trial subjects:

The clinical trial was conducted in accordance with:
- the principles of ethics as stated in the last version in use of the Declaration of Helsinki,
- the Good Clinical Practices (GCP) defined by the International Conference on Harmonization (ICH–E6, 17/07/96),
- the European directive 2001/20/CE on the conduct of clinical trials,
- Huriet's law (n° 88-1138) of December 20th, 1988, relative to the protection of persons, participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9th, 2004,
- the law on 'informatics and freedom' (Informatique et Libertés n° 78-17) of January 6th,1978 modified by the law n° 2004-801 of August 6th, 2004 relative to the protection of persons with regard to the computerized processing of personal data,
- the relevant principles of Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain
- Amended Law n° 2004-800 du 6 août 2004, relative to bioethics,
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 358
Worldwide total number of subjects	358
EEA total number of subjects	358

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)	242
From 65 to 84 years	116
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

999 patients screened:
394 patients were eligible for substudy 1, among which 175 patients were randomized, N=116 patients were randomized in arm A1 and N=59 patients in arm B1.
365 patients were eligible for substudy 2, among which 183 patie

Pre-assignment

Screening details:

Patients were considered as pre-eligible for randomisation in the substudy 1 when both following mandatory conditions were met : stable or responding disease was observed after 4 cycles of chemotherapy
and targetable alteration was identified by the Molecular Tumor Board (MTB)

Otherwise patients be oriented to the immunotherapy substudy 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A1 : Planned targeted therapy

Arm description:

Arm A1 / targeted arm: targeted maintenance from a list of targeted drugs guided by the genomic analysis.
In arm A1, N=18 patients were treated with AZD2014, N=8 with AZD4547, N=9 with AZD5363, N=6 with AZD8931, N=4 with olaparib, N=1 with savotinib, N=65 with selumitinib, and N=5 with vandetanib.

Arm type	Experimental
Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg bd, continuous dosing.

Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

80 mg bd, 2 weeks on/1 week off

Investigational medicinal product name	Capivasertib
Investigational medicinal product code	AZD5363
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

480 mg bd, 4 days on/3 days off

Investigational medicinal product name	AZD8931
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg bd, continuous dosing

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

Dosage and administration details:

300 mg bd continuous dosing

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

Dosage and administration details:

600 mg od continuous dosing (400 mg od for patient with body weight less than 50 kg)

Investigational medicinal product name	Selumetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg bd, continuous dosing

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

Dosage and administration details:

300 mg od, continuous dosing

Arm title	Arm B1: Standard maintenance therapy

Arm description:

Standard maintenance as per guidelines : with pemetrexed in non-squamous NSCLC only. In squamous NSCLC, treatment is left to the investigator’s decision as per local practice and shall be one of the 2 most common attitudes in France
1- Follow up with no active maintenance therapy
2- Gemcitabine

In arm B1: 1 patient received erlotinib, 4 patients received Gemcitabin, and 54 patients received pemetrexed.

Treatement duration: Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

Arm type	Active comparator

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 100 mg and 150 mg erlotinib (as erlotinib hydrochloride) are used in this trial.

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

Dosage and administration details:

Standard chemotherapies were prescribed as per usual practice and according to the product Summary of Product Characteristics (SmPC).

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m2, every 3 weeks

Arm title	Arm A2: MEDI4736

Arm description:

Planned immunotherapy; durvalumab

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg, every 2 weeks.

Arm title	Arm B2: Standard maintenance therapy

Arm description:

Standard maintenance as per guidelines : with pemetrexed in non-squamous NSCLC only. In squamous NSCLC, treatment is left to the investigator’s decision as per local practice and shall be one of the 2 most common attitudes in France
1- Follow up with no active maintenance therapy
2- Gemcitabine

In the Arm B2: 5 patients received Gemcitabin, 54 patients received Pemetrexed, 1 patient received Vinorelbine, and 2 patients did not receive treatment.

Treatement duration: Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

Arm type	Active comparator
Investigational medicinal product name	Gemcitabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard chemotherapies were prescribed as per usual practice and according to the product Summary

of Product Characteristics (SmPC).

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
500 mg/m2, every 3 weeks

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Treatment is left to the investigator’s decision as per local practice.

Number of subjects in period 1	Arm A1 : Planned targeted therapy	Arm B1: Standard maintenance therapy	Arm A2: MEDI4736
Started	116	59	121
Completed	1	1	10
Not completed	115	58	111
Clinical progression	2	3	1
Physician decision	1	1	4
Consent withdrawn by subject	2	1	1
Adverse event, non-fatal	15	8	12
Death	1	1	1
Other	1	-	1
Progressive disease	90	42	84
Sponsor decision	3	2	1
Alive/End Of Protocol (Completed)	-	-	6

Number of subjects in period 1	Arm B2: Standard maintenance therapy
Started	62
Completed	0
Not completed	62
Clinical progression	3
Physician decision	4
Consent withdrawn by subject	4
Adverse event, non-fatal	7
Death	3
Other	-
Progressive disease	40

Sponsor decision	1
Alive/End Of Protocol (Completed)	-

Baseline characteristics

Reporting groups

Reporting group title	Arm A1 : Planned targeted therapy

Reporting group description:

Arm A1 / targeted arm: targeted maintenance from a list of targeted drugs guided by the genomic analysis.
In arm A1, N=18 patients were treated with AZD2014, N=8 with AZD4547, N=9 with AZD5363, N=6 with AZD8931, N=4 with olaparib, N=1 with savotinib, N=65 with selumitinib, and N=5 with vandetanib.

Reporting group title	Arm B1: Standard maintenance therapy

Reporting group description:

Standard maintenance as per guidelines : with pemetrexed in non-squamous NSCLC only. In squamous NSCLC, treatment is left to the investigator's decision as per local practice and shall be one of the 2 most common attitudes in France
1- Follow up with no active maintenance therapy
2- Gemcitabine

In arm B1: 1 patient received erlotinib, 4 patients received Gemcitabin, and 54 patients received pemetrexed.

Treatement duration: Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

Reporting group title	Arm A2: MEDI4736

Reporting group description:

Planned immunotherapy; durvalumab

Reporting group title	Arm B2: Standard maintenance therapy

Reporting group description:

Standard maintenance as per guidelines : with pemetrexed in non-squamous NSCLC only. In squamous NSCLC, treatment is left to the investigator's decision as per local practice and shall be one of the 2 most common attitudes in France
1- Follow up with no active maintenance therapy
2- Gemcitabine

In the Arm B2: 5 patients received Gemcitabin, 54 patients received Pemetrexed, 1 patient received Vinorelbine, and 2 patients did not receive treatment.

Treatement duration: Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

Reporting group values	Arm A1 : Planned targeted therapy	Arm B1: Standard maintenance therapy	Arm A2: MEDI4736
Number of subjects	116	59	121
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)	88	41	78
From 65-84 years	27	18	43
85 years and over	1	0	0

Age continuous Units: years			
median	60	59	62
inter-quartile range (Q1-Q3)	55 to 64	52 to 66	53 to 67
Gender categorical Units: Subjects			
Female	46	25	48
Male	70	34	73
ECOG Units: Subjects			
ECOG 0	45	32	48
ECOG 1	71	27	73
Histological type Units: Subjects			
Non Small Cell Lung Cancer	116	59	119
Small Cell Lung Cancer	0	0	2
Histological subtype Units: Subjects			
Adenocarcinoma	102	51	107
Large Cell Carcinoma	0	1	5
Squamous Cell Carcinoma	14	6	8
Other	0	1	1
Metastatic disease Units: Subjects			
No	4	3	6
Yes	112	56	115
Number of metastatic sites at screening Units: Number			
arithmetic mean	2.9	3.0	2.8
standard deviation	± 1.3	± 1.6	± 1.41
The median time between initial diagnosis and randomization Units: Months			
median	4	4	4.3
inter-quartile range (Q1-Q3)	4 to 5	4 to 5	4 to 5

Reporting group values	Arm B2: Standard maintenance therapy	Total	
Number of subjects	62	358	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	35	242	
From 65-84 years	27	115	
85 years and over	0	1	

Age continuous Units: years			
median	62		
inter-quartile range (Q1-Q3)	52 to 68	-	
Gender categorical Units: Subjects			
Female	21	140	
Male	41	218	
ECOG Units: Subjects			
ECOG 0	19	144	
ECOG 1	43	214	
Histological type Units: Subjects			
Non Small Cell Lung Cancer	62	356	
Small Cell Lung Cancer	0	2	
Histological subtype Units: Subjects			
Adenocarcinoma	55	315	
Large Cell Carcinoma	1	7	
Squamous Cell Carcinoma	5	33	
Other	1	3	
Metastatic disease Units: Subjects			
No	3	16	
Yes	59	342	
Number of metastatic sites at screening Units: Number			
arithmetic mean	2.6		
standard deviation	± 1.1	-	
The median time between initial diagnosis and randomization Units: Months			
median	4.6		
inter-quartile range (Q1-Q3)	4 to 5	-	

End points

End points reporting groups

Reporting group title	Arm A1 : Planned targeted therapy

Reporting group description:

Arm A1 / targeted arm: targeted maintenance from a list of targeted drugs guided by the genomic analysis.
In arm A1, N=18 patients were treated with AZD2014, N=8 with AZD4547, N=9 with AZD5363, N=6 with AZD8931, N=4 with olaparib, N=1 with savotinib, N=65 with selumitinib, and N=5 with vandetanib.

Reporting group title	Arm B1: Standard maintenance therapy

Reporting group description:

Standard maintenance as per guidelines : with pemetrexed in non-squamous NSCLC only. In squamous NSCLC, treatment is left to the investigator's decision as per local practice and shall be one of the 2 most common attitudes in France
1- Follow up with no active maintenance therapy
2- Gemcitabine

In arm B1: 1 patient received erlotinib, 4 patients received Gemcitabin, and 54 patients received pemetrexed.

Treatement duration: Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

Reporting group title	Arm A2: MEDI4736

Reporting group description:

Planned immunotherapy; durvalumab

Reporting group title	Arm B2: Standard maintenance therapy

Reporting group description:

Standard maintenance as per guidelines : with pemetrexed in non-squamous NSCLC only. In squamous NSCLC, treatment is left to the investigator's decision as per local practice and shall be one of the 2 most common attitudes in France
1- Follow up with no active maintenance therapy
2- Gemcitabine

In the Arm B2: 5 patients received Gemcitabin, 54 patients received Pemetrexed, 1 patient received Vinorelbine, and 2 patients did not receive treatment.

Treatement duration: Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression-free survival in the targeted drug arm compared to standard maintenance therapy arm. PFS was defined as the time from randomization to the first documented progression of disease or death, whatever the cause. Patients still alive at the time of analysis without documented progression (including lost of follow-up) were censored at the last known alive date (primary endpoint of substudy 1).

End point type	Primary

End point timeframe:

from randomization to disease progression or death from any cause, whichever comes first, up to 16 months.

End point values	Arm A1 : Planned targeted therapy	Arm B1: Standard maintenance therapy	Arm A2: MEDI4736	Arm B2: Standard maintenance therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	116	59	121	62
Units: Months				
number (confidence interval 95%)	2.7 (1.6 to 2.9)	2.7 (1.6 to 4.1)	3.0 (2.3 to 4.4)	3.0 (2.0 to 5.1)

Statistical analyses

Statistical analysis title	PFS analysis (substudy 1)

Statistical analysis description:

The Cox regression analysis was then adjusted for the factors used as stratification variables in the randomization.
There was no difference between arm A1 and arm B1 according to treatment, histological subtype, disease status at randomization, smoking status, and molecular alteration category.

Comparison groups	Arm A1 : Planned targeted therapy v Arm B1: Standard maintenance therapy
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.8691
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.36

Statistical analysis title	PFS analysis (substudy 2)

Statistical analysis description:

The Cox regression analysis was then adjusted for the factors used as stratification variables in the randomization. The results showed a difference base on histological subtypes (squamous vs non-squamous; p=8.5e-05) but no difference was observed between arm A2 and arm B2 according to treatment, disease status at randomization, and smoking status.

Comparison groups	Arm A2: MEDI4736 v Arm B2: Standard maintenance therapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.379
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.2

Secondary: Overall survival (OS) in both arms

End point title	Overall survival (OS) in both arms

End point description:

OS in each substudy. OS was defined as the time from randomization to death due to any cause. Patients still alive at the time of analysis (including lost of follow-up) were censored at the last known alive date.

End point type	Secondary

End point timeframe:

from randomization to death (any cause), up to 16 months.

End point values	Arm A1 : Planned targeted therapy	Arm B1: Standard maintenance therapy	Arm A2: MEDI4736	Arm B2: Standard maintenance therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	116	59	121	62
Units: Months				
median (confidence interval 95%)	14.3 (11.0 to 18.3)	14.1 (8.0 to 30.9)	17.0 (12.1 to 19.5)	14.9 (10.5 to 22.0)

Statistical analyses

Statistical analysis title	OS analysis (Substudy 1)

Statistical analysis description:

There was no difference in OS based on treatments, histological subtypes, smoking status, and molecular alterations.
There was a difference according to disease status at randomization (p=0.0325).

Comparison groups	Arm A1 : Planned targeted therapy v Arm B1: Standard maintenance therapy
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.8719
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.55

Statistical analysis title	OS analysis (Substudy 2)

Statistical analysis description:

There were no overall survival differences based on treatments, disease status at randomization, and smoking status.
There was a difference according to histological subtypes (squamous vs non-squamous; p=0.007).

Comparison groups	Arm A2: MEDI4736 v Arm B2: Standard maintenance therapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.728
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.4

Secondary: ORR

End point title	ORR

End point description:

To compare overall response rates (ORR) and changes in tumor size in each substudy.

End point type	Secondary

End point timeframe:

Tumor response is assessed every 21 days from treatment initiation until first progression or death from any cause, whichever comes first, up to 16 months

End point values	Arm A1 : Planned targeted therapy	Arm B1: Standard maintenance therapy	Arm A2: MEDI4736	Arm B2: Standard maintenance therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	116	59	121	62
Units: percent				
number (not applicable)				
CR/PR	5.3	10.5	14.3	3.6
PD/SD	94.7	89.5	85.7	96.4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Toxicities will be assessed during the whole treatment period (4 months expected in average) followed by a 1-year post-treatment follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Arm A1
Reporting group description: -	
Reporting group title	Arm B1
Reporting group description: -	
Reporting group title	Arm A2
Reporting group description: -	
Reporting group title	Arm B2

Reporting group description: -

Serious adverse events	Arm A1	Arm B1	Arm A2
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 175 (12.00%)	14 / 59 (23.73%)	19 / 121 (15.70%)
number of deaths (all causes)	78	37	72
number of deaths resulting from adverse events	1		1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Superficial basal cell carcinoma			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Intracardiac thrombus			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (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
Ischemic stroke			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peripheral arterial disease			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Thromboembolic event			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Transient ischaemic attack			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Aplasia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Catheter site extravasation			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Disease progression			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Fever			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flu-like symptoms			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Hyperthermia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Malaise			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden death, cause unknown			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Thoracic pain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Immune system disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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

Chest tightness			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (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
Dyspnea			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hemoptysis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Interstitial lung disease			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural effusion			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonitis			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumopathy			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Injury, poisoning and procedural complications			
Fracture of scapula			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Myopericarditis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial tamponade			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pericarditis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Confusional state			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Stroke			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia aggravated			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Aplasia bone marrow			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Febrile aplasia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 175 (0.00%)	2 / 59 (3.39%)	0 / 121 (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

Febrile neutropenia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Cardiac arrest			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Eye disorders			
Central retinal vein occlusion			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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
Diverticulitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Sigmoiditis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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

Hepatobiliary disorders			
Acute calculous cholecystitis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (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			
Toxicodermia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macroscopic hematuria			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 175 (0.00%)	2 / 59 (3.39%)	0 / 121 (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
Costal pain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (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
Humerus fracture			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rheumatoid arthritis flare up			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (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
Haemophilus pneumonia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Perineal abscess			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal pneumonia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary infection			

subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (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			
Hyponatremia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (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
Anorexia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Serious adverse events	Arm B2		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 62 (20.97%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Superficial basal cell carcinoma			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Intracardiac thrombus			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischemic stroke			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial disease			

subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thromboembolic event				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Aplasia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Catheter site extravasation				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Flu-like symptoms				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hyperthermia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death, cause unknown			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thoracic pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Chest tightness				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnea				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemoptysis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Interstitial lung disease				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumopathy				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture of scapula			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myopericarditis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial tamponade			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pericarditis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Confusional state			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stroke			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia aggravated			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aplasia bone marrow			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile aplasia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Febrile neutropenia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Central retinal vein occlusion			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sigmoiditis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Acute calculous cholecystitis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxicodermia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Macroscopic hematuria			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Costal pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			

subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rheumatoid arthritis flare up				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemophilus pneumonia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perineal abscess				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumococcal pneumonia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary infection				

subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anorexia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm A1	Arm B1	Arm A2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 175 (64.57%)	53 / 59 (89.83%)	112 / 121 (92.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Atypical Fibroxanthoma			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	3
Metastases To Meninges			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Metastatic Pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Thyroid Neoplasm			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	2
Vascular disorders			
Capillary Fragility			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0

Deep Vein Thrombosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Hot Flush			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	4	0
Hypertension			
subjects affected / exposed	12 / 175 (6.86%)	2 / 59 (3.39%)	4 / 121 (3.31%)
occurrences (all)	21	3	6
Phlebitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Thrombosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Collateral Circulation			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	3
Embolism			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	2
Hypotension			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Intermittent Claudication			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	4
Lymphoedema			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	3
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1

Superior Vena Cava Syndrome			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Vascular Pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Venous Insufficiency			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Nutritional			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Tooth Extraction			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	1	0	2
Prophylaxis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	40 / 175 (22.86%)	17 / 59 (28.81%)	45 / 121 (37.19%)
occurrences (all)	126	58	191
Chest Pain			
subjects affected / exposed	12 / 175 (6.86%)	8 / 59 (13.56%)	22 / 121 (18.18%)
occurrences (all)	25	12	61
Chills			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	6	0	1
Crepitations			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Face Oedema			
subjects affected / exposed	9 / 175 (5.14%)	2 / 59 (3.39%)	1 / 121 (0.83%)
occurrences (all)	13	8	1
Fatigue			

subjects affected / exposed	20 / 175 (11.43%)	12 / 59 (20.34%)	16 / 121 (13.22%)
occurrences (all)	43	33	57
Feeling Cold			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
General Physical Health deterioration			
subjects affected / exposed	0 / 175 (0.00%)	2 / 59 (3.39%)	1 / 121 (0.83%)
occurrences (all)	0	2	1
Generalised Oedema			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Hyperthermia			
subjects affected / exposed	1 / 175 (0.57%)	2 / 59 (3.39%)	2 / 121 (1.65%)
occurrences (all)	1	3	1
Impaired Healing			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Influenza Like Illness			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	5 / 121 (4.13%)
occurrences (all)	0	1	7
Malaise			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Mucosal Inflammation			
subjects affected / exposed	16 / 175 (9.14%)	1 / 59 (1.69%)	3 / 121 (2.48%)
occurrences (all)	21	2	3
Mucosal Toxicity			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Oedema			
subjects affected / exposed	31 / 175 (17.71%)	12 / 59 (20.34%)	6 / 121 (4.96%)
occurrences (all)	126	26	17
Oedema Peripheral			
subjects affected / exposed	17 / 175 (9.71%)	7 / 59 (11.86%)	4 / 121 (3.31%)
occurrences (all)	41	16	13
Pain			

subjects affected / exposed	15 / 175 (8.57%)	6 / 59 (10.17%)	17 / 121 (14.05%)
occurrences (all)	23	32	37
Peripheral Swelling			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	12 / 175 (6.86%)	3 / 59 (5.08%)	14 / 121 (11.57%)
occurrences (all)	16	3	16
Sudden Death			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Xerosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Chest Discomfort			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Facial pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Sarcoidosis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	7
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Erectile Dysfunction			

subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Balanoposthitis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	24 / 175 (13.71%)	7 / 59 (11.86%)	0 / 121 (0.00%)
occurrences (all)	40	11	0
Dysphonia			
subjects affected / exposed	5 / 175 (2.86%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	8	0	0
Dyspnoea			
subjects affected / exposed	32 / 175 (18.29%)	12 / 59 (20.34%)	0 / 121 (0.00%)
occurrences (all)	59	19	0
Epistaxis			
subjects affected / exposed	6 / 175 (3.43%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	7	1	0
Haemoptysis			
subjects affected / exposed	3 / 175 (1.71%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	3	1	0
Hypoxia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Lung Disorder			
subjects affected / exposed	3 / 175 (1.71%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	4	1	0
Nasal Dryness			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Pleuritic Pain			

subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	5 / 175 (2.86%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	7	1	0
Productive Cough			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Pulmonary Embolism			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	2	1	0
Pulmonary Haemorrhage			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Pulmonary Pneumatocele			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Rhinitis Allergic			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	12	1	0
Rhinorrhoea			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	3	1	0
Wheezing			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	4 / 121 (3.31%)
occurrences (all)	4	1	7
Confusional State			
subjects affected / exposed	0 / 175 (0.00%)	2 / 59 (3.39%)	0 / 121 (0.00%)
occurrences (all)	0	2	0

Delirium			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	1	0	2
Hallucination			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	6 / 175 (3.43%)	2 / 59 (3.39%)	4 / 121 (3.31%)
occurrences (all)	11	12	10
Irritability			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Libido Decreased			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Sleep Disorder			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Logorrhoea			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	15
Investigations			
Alanine Aminotransferase increased			
subjects affected / exposed	5 / 175 (2.86%)	8 / 59 (13.56%)	2 / 121 (1.65%)
occurrences (all)	17	8	9
Aspartate Aminotransferase			
subjects affected / exposed	6 / 175 (3.43%)	6 / 59 (10.17%)	4 / 121 (3.31%)
occurrences (all)	22	6	6
Blood Alkaline Phosphatase			

subjects affected / exposed	2 / 175 (1.14%)	2 / 59 (3.39%)	0 / 121 (0.00%)
occurrences (all)	3	6	0
Blood Cholesterol			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Blood Creatine			
subjects affected / exposed	5 / 175 (2.86%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	11	0	4
Blood Creatinine Increased			
subjects affected / exposed	6 / 175 (3.43%)	2 / 59 (3.39%)	10 / 121 (8.26%)
occurrences (all)	11	3	16
Blood Lactate			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	2 / 121 (1.65%)
occurrences (all)	4	1	3
Blood Phosphorus			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	6	0	0
Blood Pressure Increased			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	6	0	10
Blood Urea Increased			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Creatinine Renal Clearance			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	0	1	1
Electrocardiogram Qt			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Intestinal Transit Time			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Lipase Increased			

subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	6 / 121 (4.96%)
occurrences (all)	0	1	24
Platelet Count Decreased			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	1	1	1
Platelet Count Increased			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Protein Total Decreased			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Transaminases Increased			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Troponin			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Weight Decreased			
subjects affected / exposed	3 / 175 (1.71%)	3 / 59 (5.08%)	5 / 121 (4.13%)
occurrences (all)	3	3	6
Weight Increased			
subjects affected / exposed	4 / 175 (2.29%)	1 / 59 (1.69%)	5 / 121 (4.13%)
occurrences (all)	5	2	10
Amino Acid Level Increased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Amylase Increased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	10 / 121 (8.26%)
occurrences (all)	0	0	34
Blood Thyroid Stimulating Hormone			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	5
Breath Sounds Abnormal			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	8
Cardiac Murmur			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	3
Eosinophil Count Increased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	2
Gamma-Glutamyltransferase			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	6 / 121 (4.96%)
occurrences (all)	0	0	18
Haemoglobin Decreased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
High Density Lipoprotein Increased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Thyroxine Increased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	2
Vitamin D Decreased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Frostbite			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Eye Burns			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Ligament Sprain			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	2
Limb Injury			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Scapula Fracture			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	4
Skin Injury			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Ichthyosis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	2	0	1
Atrial Fibrillation			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Coronary Artery Disease			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Extrasystoles			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Pericardial Effusion			

subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	2	0	3
Tachycardia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	0	1	2
Atrioventricular Block First Degree			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Cardiac Arrest			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Myocardial Infarction			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Myocarditis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Ataxia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Balance Disorder			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	5	0	0
Dizziness			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	2 / 121 (1.65%)
occurrences (all)	2	1	2
Dysaesthesia			
subjects affected / exposed	1 / 175 (0.57%)	2 / 59 (3.39%)	0 / 121 (0.00%)
occurrences (all)	1	2	0

Dysarthria			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	7 / 175 (4.00%)	2 / 59 (3.39%)	1 / 121 (0.83%)
occurrences (all)	33	3	1
Dyskinesia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Facial Paralysis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	10 / 175 (5.71%)	0 / 59 (0.00%)	16 / 121 (13.22%)
occurrences (all)	17	0	59
Ischaemic Stroke			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Language Disorder			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	2	0
Nervous System Disorder			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 175 (0.00%)	2 / 59 (3.39%)	2 / 121 (1.65%)
occurrences (all)	0	14	2
Neuropathy Peripheral			
subjects affected / exposed	6 / 175 (3.43%)	5 / 59 (8.47%)	7 / 121 (5.79%)
occurrences (all)	19	24	27
Paraesthesia			
subjects affected / exposed	8 / 175 (4.57%)	7 / 59 (11.86%)	9 / 121 (7.44%)
occurrences (all)	31	17	16
Peripheral Sensory			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0

Restless Legs Syndrome			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Sciatica			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	3 / 121 (2.48%)
occurrences (all)	4	2	5
Tremor			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	2	0	1
Allodynia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Aphonia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Convulsion			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Dropped Head Syndrome			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	4
Olfactory Nerve Disorder			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Viith Nerve Paralysis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	20 / 175 (11.43%)	20 / 59 (33.90%)	18 / 121 (14.88%)
occurrences (all)	52	57	48
Bicytopenia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Bone Marrow Failure			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Eosinophilia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	9	0	0
Febrile Neutropenia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	1 / 175 (0.57%)	3 / 59 (5.08%)	0 / 121 (0.00%)
occurrences (all)	1	3	0
Lymphopenia			
subjects affected / exposed	0 / 175 (0.00%)	2 / 59 (3.39%)	2 / 121 (1.65%)
occurrences (all)	0	2	5
Neutropenia			
subjects affected / exposed	1 / 175 (0.57%)	8 / 59 (13.56%)	2 / 121 (1.65%)
occurrences (all)	2	15	6
Thrombocytopenia			
subjects affected / exposed	1 / 175 (0.57%)	6 / 59 (10.17%)	2 / 121 (1.65%)
occurrences (all)	1	8	2
Thrombocytosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	22	0	4
Ear Pain			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	2	2	0

Hypoacusis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	7 / 175 (4.00%)	1 / 59 (1.69%)	2 / 121 (1.65%)
occurrences (all)	46	2	2
Vertigo			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	6 / 121 (4.96%)
occurrences (all)	4	0	12
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Conjunctival Haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Dry Eye			
subjects affected / exposed	5 / 175 (2.86%)	3 / 59 (5.08%)	1 / 121 (0.83%)
occurrences (all)	11	9	1
Eye Disorder			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Eye Pain			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Eye Swelling			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Eyelid Oedema			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	6	0	0
Lacrimation Increased			
subjects affected / exposed	3 / 175 (1.71%)	3 / 59 (5.08%)	0 / 121 (0.00%)
occurrences (all)	11	6	0
Ocular Hypertension			

subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Periorbital Oedema			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Photopsia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Retinal Detachment			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	10	0	0
Retinal Vein Occlusion			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Retinopathy			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Serous Retinal			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Vsion Blurred			
subjects affected / exposed	6 / 175 (3.43%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	10	0	3
Visual Acuity Reduced			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Visual Impairment			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	2	1	3
Xerophthalmia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Blindness			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Diplopia			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	9
Eye Irritation			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Eye Oedema			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Eyelid Skin Dryness			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	0	0	4
Vitreous Floaters			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Abdominal Pain			
subjects affected / exposed	11 / 175 (6.29%)	3 / 59 (5.08%)	8 / 121 (6.61%)
occurrences (all)	17	3	17
Abdominal Pain Upper			
subjects affected / exposed	9 / 175 (5.14%)	5 / 59 (8.47%)	5 / 121 (4.13%)
occurrences (all)	24	18	7
Anal Haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	17 / 175 (9.71%)	8 / 59 (13.56%)	16 / 121 (13.22%)
occurrences (all)	30	12	37
Diarrhoea			
subjects affected / exposed	35 / 175 (20.00%)	7 / 59 (11.86%)	20 / 121 (16.53%)
occurrences (all)	95	8	45
Dry Mouth			
subjects affected / exposed	7 / 175 (4.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	11	0	2

Dyspepsia			
subjects affected / exposed	6 / 175 (3.43%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	8	0	1
Dysphagia			
subjects affected / exposed	2 / 175 (1.14%)	2 / 59 (3.39%)	2 / 121 (1.65%)
occurrences (all)	5	2	5
Functional			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Disorder			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Motility			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal Reflux			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	8	0	4
Haemorrhoids			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Mouth Ulceration			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	3	0	1
Nausea			
subjects affected / exposed	30 / 175 (17.14%)	17 / 59 (28.81%)	14 / 121 (11.57%)
occurrences (all)	55	31	31
Noninfective Gingivitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Odynophagia			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	4	0	1
Oesophagitis			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	5	0	0

Reflux Gastritis			
subjects affected / exposed	3 / 175 (1.71%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	16	1	0
Salivary Hypersecretion			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	4 / 175 (2.29%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	7	0	0
Vomiting			
subjects affected / exposed	19 / 175 (10.86%)	6 / 59 (10.17%)	5 / 121 (4.13%)
occurrences (all)	28	10	8
Aerophagia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Anal Fissure			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal Pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Inguinal Hernia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Rectal Haemorrhage			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Subileus			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Tongue Oedema			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1

Toothache			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	4 / 121 (3.31%)
occurrences (all)	1	0	7
Hepatocellular Injury			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	3 / 121 (2.48%)
occurrences (all)	11	1	4
Hyperbilirubinaemia			
subjects affected / exposed	0 / 175 (0.00%)	3 / 59 (5.08%)	0 / 121 (0.00%)
occurrences (all)	0	3	0
Cholecystitis Acute			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Hepatomegaly			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 175 (2.86%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	14	0	0
Alopecia			
subjects affected / exposed	7 / 175 (4.00%)	2 / 59 (3.39%)	4 / 121 (3.31%)
occurrences (all)	18	2	4
Dermatitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Dermatitis Acneiform			
subjects affected / exposed	13 / 175 (7.43%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	31	0	1
Dry Skin			
subjects affected / exposed	25 / 175 (14.29%)	3 / 59 (5.08%)	13 / 121 (10.74%)
occurrences (all)	71	4	34
Eczema			

subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	3	0	4
Erythema			
subjects affected / exposed	12 / 175 (6.86%)	1 / 59 (1.69%)	4 / 121 (3.31%)
occurrences (all)	45	1	6
Hypertrichosis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Ichthyosis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Lividity			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Nail Discolouration			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Nail Disorder			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	10	0	6
Nail Ridging			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Nail Toxicity			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	7	0	1
Night Sweats			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	5 / 121 (4.13%)
occurrences (all)	3	0	9
Onychoclasis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Onycholysis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	6	0	0
Palmar-Plantar			

subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	6	0	0
Photosensitivity Reaction			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	14 / 175 (8.00%)	1 / 59 (1.69%)	18 / 121 (14.88%)
occurrences (all)	19	1	66
Rash			
subjects affected / exposed	48 / 175 (27.43%)	3 / 59 (5.08%)	10 / 121 (8.26%)
occurrences (all)	167	5	44
Rash Follicular			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	18	0	0
Rash Macular			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Rash Maculo-Papular			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	7	0	1
Rash Pruritic			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Skin Fissures			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	5	0	0
Skin Lesion			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	5	0	1
Skin Toxicity			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Stasis Dermatitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	2	0
Actinic Keratosis			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	2
Cutaneous Sarcoidosis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	8
Intertrigo			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Macule			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Pigmentation Disorder			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Rash Erythematous			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	2
Rash Papular			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Skin Exfoliation			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Skin Induration			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Skin Mass			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	4
Vitiligo			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	11
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0

Dysuria			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	4 / 175 (2.29%)	2 / 59 (3.39%)	1 / 121 (0.83%)
occurrences (all)	8	2	1
Proteinuria			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Renal Failure			
subjects affected / exposed	5 / 175 (2.86%)	3 / 59 (5.08%)	2 / 121 (1.65%)
occurrences (all)	8	4	2
Renal Impairment			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	1	1	0
Renal Pain			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Ureteral Disorder			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Urinary Incontinence			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	4
Urinary Retention			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	8 / 121 (6.61%)
occurrences (all)	1	0	19
Hyperthyroidism			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	9 / 121 (7.44%)
occurrences (all)	0	0	24
Thyroid Disorder			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	9
Thyroiditis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 175 (6.29%)	3 / 59 (5.08%)	18 / 121 (14.88%)
occurrences (all)	26	5	113
Back Pain			
subjects affected / exposed	13 / 175 (7.43%)	3 / 59 (5.08%)	15 / 121 (12.40%)
occurrences (all)	23	4	51
Bone Pain			
subjects affected / exposed	2 / 175 (1.14%)	2 / 59 (3.39%)	9 / 121 (7.44%)
occurrences (all)	2	3	15
Flank Pain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	5	0
Hypercreatinaemia			
subjects affected / exposed	0 / 175 (0.00%)	3 / 59 (5.08%)	3 / 121 (2.48%)
occurrences (all)	0	3	19
Joint Stiffness			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Joint Swelling			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Muscle Spasms			
subjects affected / exposed	5 / 175 (2.86%)	0 / 59 (0.00%)	4 / 121 (3.31%)
occurrences (all)	12	0	13
Muscular Weakness			

subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	2 / 121 (1.65%)
occurrences (all)	2	1	2
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 175 (1.14%)	2 / 59 (3.39%)	2 / 121 (1.65%)
occurrences (all)	4	2	2
Musculoskeletal Pain			
subjects affected / exposed	3 / 175 (1.71%)	3 / 59 (5.08%)	13 / 121 (10.74%)
occurrences (all)	4	4	44
Myalgia			
subjects affected / exposed	10 / 175 (5.71%)	1 / 59 (1.69%)	8 / 121 (6.61%)
occurrences (all)	22	1	16
Neck Pain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	7 / 121 (5.79%)
occurrences (all)	0	1	31
Pain In Extremity			
subjects affected / exposed	7 / 175 (4.00%)	3 / 59 (5.08%)	6 / 121 (4.96%)
occurrences (all)	17	5	10
Periarthritis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	0	1	3
Rheumatoid Arthritis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Spinal Pain			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	4 / 121 (3.31%)
occurrences (all)	1	2	16
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Myositis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Nuchal Rigidity			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Osteoarthritis			

subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	6
Tendonitis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Torticollis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Infections and infestations			
Arthritis Bacterial			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	7 / 175 (4.00%)	6 / 59 (10.17%)	10 / 121 (8.26%)
occurrences (all)	9	8	15
Candida Infection			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Cellulitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	4 / 175 (2.29%)	4 / 59 (6.78%)	7 / 121 (5.79%)
occurrences (all)	4	7	17
Device Related Infection			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Diverticulitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	2	0
Ear Infection			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Eye Infection			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0

Folliculitis			
subjects affected / exposed	12 / 175 (6.86%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	47	2	2
Fungal Infection			
subjects affected / exposed	4 / 175 (2.29%)	1 / 59 (1.69%)	2 / 121 (1.65%)
occurrences (all)	6	1	3
Gastroenteritis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	1
Gingival Abscess			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Herpes Zoster			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	3	0	1
Hordeolum			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	1	0	2
Lung Infection			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	1	1	1
Nail Infection			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	2	0	2
Onychomycosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Oral Fungal Infection			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0

Oral Herpes			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	9 / 175 (5.14%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	29	0	1
Periodontitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	4	0	0
Pneumonia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	1	0	3
Pyelonephritis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Rash Pustular			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Respiratory Tract Infection			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	6 / 175 (3.43%)	3 / 59 (5.08%)	7 / 121 (5.79%)
occurrences (all)	8	4	7
Sinusitis			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	2	0	2
Skin Infection			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Tooth Abscess			
subjects affected / exposed	2 / 175 (1.14%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	3	1	0

Urinary Tract Infection			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	4	0	4
Vulvovaginal Candidiasis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal Mycotic			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Abscess			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Periumbilical Abscess			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Spinal Cord Infection			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	2 / 121 (1.65%)
occurrences (all)	0	0	3
Viral Infection			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 175 (0.57%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	1	1	0
Cell Death			

subjects affected / exposed	4 / 175 (2.29%)	1 / 59 (1.69%)	4 / 121 (3.31%)
occurrences (all)	6	2	10
Decreased Appetite			
subjects affected / exposed	21 / 175 (12.00%)	7 / 59 (11.86%)	20 / 121 (16.53%)
occurrences (all)	40	12	33
Dehydration			
subjects affected / exposed	0 / 175 (0.00%)	1 / 59 (1.69%)	0 / 121 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	2 / 175 (1.14%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	2	0	4
Hypercholesterolaemia			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Hypercreatinaemia			
subjects affected / exposed	0 / 175 (0.00%)	3 / 59 (5.08%)	6 / 121 (4.96%)
occurrences (all)	0	3	21
Hyperglycaemia			
subjects affected / exposed	6 / 175 (3.43%)	1 / 59 (1.69%)	2 / 121 (1.65%)
occurrences (all)	10	1	4
Hyperkalaemia			
subjects affected / exposed	3 / 175 (1.71%)	1 / 59 (1.69%)	4 / 121 (3.31%)
occurrences (all)	3	2	6
Hypermagnesaemia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	2	0	0
Hypoalbuminaemia			
subjects affected / exposed	4 / 175 (2.29%)	1 / 59 (1.69%)	1 / 121 (0.83%)
occurrences (all)	11	1	1
Hypoglycaemia			

subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	3 / 121 (2.48%)
occurrences (all)	1	0	14
Hypomagnesaemia			
subjects affected / exposed	6 / 175 (3.43%)	0 / 59 (0.00%)	4 / 121 (3.31%)
occurrences (all)	10	0	5
Hyponatraemia			
subjects affected / exposed	3 / 175 (1.71%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	3	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Hypoproteinaemia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 59 (0.00%)	0 / 121 (0.00%)
occurrences (all)	1	0	0
Malnutrition			
subjects affected / exposed	0 / 175 (0.00%)	0 / 59 (0.00%)	1 / 121 (0.83%)
occurrences (all)	0	0	1

Non-serious adverse events	Arm B2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 62 (88.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Atypical Fibroxanthoma			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Metastases To Meninges			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Metastatic Pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Thyroid Neoplasm			

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Capillary Fragility			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Deep Vein Thrombosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hot Flush			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Phlebitis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Thrombosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Collateral Circulation			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Embolism			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Intermittent Claudication			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		

Lymphoedema subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Peripheral Arterial Occlusive Disease subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Superior Vena Cava Syndrome subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Vascular Pain subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 2		
Venous Insufficiency subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Surgical and medical procedures Nutritional subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Tooth Extraction subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Prophylaxis subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	33 / 62 (53.23%) 73		
Chest Pain subjects affected / exposed occurrences (all)	9 / 62 (14.52%) 19		
Chills subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1		
Crepitations			

subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Face Oedema				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	15 / 62 (24.19%)			
occurrences (all)	39			
Feeling Cold				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
General Physical Health deterioration				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	3			
Generalised Oedema				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hyperthermia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Impaired Healing				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Influenza Like Illness				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Malaise				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Mucosal Inflammation				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Mucosal Toxicity				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Oedema				

subjects affected / exposed	12 / 62 (19.35%)		
occurrences (all)	22		
Oedema Peripheral			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	19		
Pain			
subjects affected / exposed	9 / 62 (14.52%)		
occurrences (all)	10		
Peripheral Swelling			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	4		
Sudden Death			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Xerosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Chest Discomfort			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Facial pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Sarcoidosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		

Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Erectile Dysfunction			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Balanoposthitis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Lung Disorder			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Nasal Dryness			

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pleuritic Pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Productive Cough			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pulmonary Embolism			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pulmonary Haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pulmonary Pneumatocele			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Rhinitis Allergic			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		

Confusional State			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Delirium			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	4		
Hallucination			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	8		
Irritability			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Libido Decreased			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Sleep Disorder			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Logorrhoea			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Nightmare			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine Aminotransferase increased			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	4		
Aspartate Aminotransferase			

subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	5			
Blood Alkaline Phosphatase				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Blood Cholesterol				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Blood Creatine				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Blood Creatinine Increased				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	9			
Blood Lactate				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Blood Phosphorus				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Blood Pressure Increased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	9			
Blood Urea Increased				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Creatinine Renal Clearance				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Electrocardiogram Qt				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hepatic Enzyme Increased				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Intestinal Transit Time				

subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Lipase Increased				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Platelet Count Decreased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Platelet Count Increased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Protein Total Decreased				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Transaminases Increased				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Troponin				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Weight Decreased				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	3			
Weight Increased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Amino Acid Level Increased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Amylase Increased				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Blood Thyroid Stimulating Hormone				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Breath Sounds Abnormal				

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Cardiac Murmur			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Eosinophil Count Increased			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	10		
Haemoglobin Decreased			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
High Density Lipoprotein Increased			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Thyroxine Increased			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Vitamin D Decreased			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Frostbite			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Eye Burns			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Fracture			

subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Ligament Sprain subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Limb Injury subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Scapula Fracture subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Skin Injury subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Congenital, familial and genetic disorders Aplasia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Ichthyosis subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Cardiac disorders Angina Pectoris subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Atrial Fibrillation subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Bradycardia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Coronary Artery Disease subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Extrasystoles			

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Pericardial Effusion			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Atrioventricular Block First Degree			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Cardiac Arrest			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Myocardial Infarction			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Myocarditis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Ataxia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Balance Disorder			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	2		
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	2		

Dysaesthesia				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	3			
Dysarthria				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Dysgeusia				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	4			
Dyskinesia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Facial Paralysis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Headache				
subjects affected / exposed	4 / 62 (6.45%)			
occurrences (all)	4			
Ischaemic Stroke				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Language Disorder				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nervous System Disorder				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Neuralgia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Neuropathy Peripheral				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Paraesthesia				
subjects affected / exposed	5 / 62 (8.06%)			
occurrences (all)	21			

Peripheral Sensory				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Restless Legs Syndrome				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Sciatica				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Tremor				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Allodynia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Aphonia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Convulsion				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Dropped Head Syndrome				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hypoaesthesia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	2			
Olfactory Nerve Disorder				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Syncope				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Viith Nerve Paralysis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 62 (25.81%)		
occurrences (all)	45		
Bicytopenia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Bone Marrow Failure			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Eosinophilia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Febrile Neutropenia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Thrombocytosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Ear Pain			

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypoacusis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	8		
Vertigo			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Conjunctival Haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Dry Eye			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	2		
Eye Disorder			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Eye Pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Eye Swelling			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Eyelid Oedema			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	2		
Lacrimation Increased			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	42		

Ocular Hypertension				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Periorbital Oedema				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	9			
Photopsia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Retinal Detachment				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Retinal Vein Occlusion				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Retinopathy				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Serous Retinal				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Vsion Blurred				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Visual Acuity Reduced				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Visual Impairment				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Xerophthalmia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Blindness				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	2			

Diplopia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Eye Irritation				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Eye Oedema				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	5			
Eyelid Skin Dryness				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Vitreous Floaters				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Gastrointestinal disorders				
Abdominal Distension				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Abdominal Pain				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	3			
Abdominal Pain Upper				
subjects affected / exposed	4 / 62 (6.45%)			
occurrences (all)	8			
Anal Haemorrhage				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	9 / 62 (14.52%)			
occurrences (all)	18			
Diarrhoea				
subjects affected / exposed	8 / 62 (12.90%)			
occurrences (all)	13			
Dry Mouth				

subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Dysphagia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Functional				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Gastrointestinal Disorder				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Gastrointestinal Motility				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Gastrooesophageal Reflux				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Haemorrhoids				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Mouth Ulceration				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	17 / 62 (27.42%)			
occurrences (all)	33			
Noninfective Gingivitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Odynophagia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Oesophagitis				

subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Reflux Gastritis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Salivary Hypersecretion				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Stomatitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Vomiting				
subjects affected / exposed	9 / 62 (14.52%)			
occurrences (all)	19			
Aerophagia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Anal Fissure				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	3			
Colitis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Gastrointestinal Pain				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Inguinal Hernia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Rectal Haemorrhage				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Subileus				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Tongue Oedema				

subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0 2 / 62 (3.23%) 3		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all) Hepatocellular Injury subjects affected / exposed occurrences (all) Hyperbilirubinaemia subjects affected / exposed occurrences (all) Cholecystitis Acute subjects affected / exposed occurrences (all) Hepatomegaly subjects affected / exposed occurrences (all)	 0 / 62 (0.00%) 0 3 / 62 (4.84%) 8 0 / 62 (0.00%) 0 1 / 62 (1.61%) 1 0 / 62 (0.00%) 0		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all) Dermatitis subjects affected / exposed occurrences (all) Dermatitis Acneiform subjects affected / exposed occurrences (all) Dry Skin	 0 / 62 (0.00%) 0 1 / 62 (1.61%) 9 0 / 62 (0.00%) 0 0 / 62 (0.00%) 0		

subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	6			
Eczema				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Hypertrichosis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Ichthyosis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Lividity				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nail Discolouration				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nail Disorder				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nail Ridging				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nail Toxicity				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Night Sweats				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Onychoclasis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Onycholysis				

subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Palmar-Plantar				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Photosensitivity Reaction				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Rash				
subjects affected / exposed	7 / 62 (11.29%)			
occurrences (all)	9			
Rash Follicular				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Rash Macular				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Rash Maculo-Papular				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Rash Pruritic				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Skin Fissures				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Skin Lesion				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Skin Toxicity				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Stasis Dermatitis				

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Actinic Keratosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Cutaneous Sarcoidosis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Intertrigo			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Macule			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	2		
Pigmentation Disorder			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Rash Erythematous			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Rash Papular			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Skin Exfoliation			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Skin Induration			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Skin Mass			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Vitiligo			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			

Acute Kidney Injury subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Dysuria subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Haematuria subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1		
Proteinuria subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1		
Renal Failure subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 8		
Renal Impairment subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Renal Pain subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Ureteral Disorder subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Urinary Incontinence subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Pollakiuria subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Urinary Retention subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 3		
Endocrine disorders Hypothyroidism			

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hyperthyroidism			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Thyroid Disorder			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Thyroiditis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Back Pain			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	15		
Bone Pain			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	7		
Flank Pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypercreatinaemia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Joint Stiffness			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Joint Swelling			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Muscle Spasms			

subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Muscular Weakness				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Musculoskeletal Chest Pain				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Musculoskeletal Pain				
subjects affected / exposed	5 / 62 (8.06%)			
occurrences (all)	5			
Myalgia				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	5			
Neck Pain				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Pain In Extremity				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Periarthritis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Rheumatoid Arthritis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Spinal Pain				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Musculoskeletal Stiffness				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Myositis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nuchal Rigidity				

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	3		
Torticollis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Arthritis Bacterial			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Candida Infection			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	13		
Device Related Infection			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Diverticulitis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Ear Infection			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		

Eye Infection				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Folliculitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Fungal Infection				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Gingival Abscess				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Herpes Zoster				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hordeolum				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Lung Infection				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nail Infection				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Onychomycosis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			

Oral Fungal Infection				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Oral Herpes				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Periodontitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Pyelonephritis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Rash Pustular				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Skin Infection				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			

Tooth Abscess subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1		
Vulvovaginal Candidiasis subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Vulvovaginal Mycotic subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Abscess subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Laryngitis subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1		
Periumbilical Abscess subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Sepsis subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Spinal Cord Infection subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1		
Tracheitis subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Viral Infection subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Metabolism and nutrition disorders Cachexia			

subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Cell Death				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences (all)	5			
Decreased Appetite				
subjects affected / exposed	14 / 62 (22.58%)			
occurrences (all)	18			
Dehydration				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	1			
Hypercalcaemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hypercholesterolaemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hypercreatinaemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hyperglycaemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hyperkalaemia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences (all)	2			
Hypermagnesaemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hyperphosphataemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hyperuricaemia				
subjects affected / exposed	0 / 62 (0.00%)			
occurrences (all)	0			
Hypoalbuminaemia				

subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hypoproteinaemia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Malnutrition			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2014	- Modification of the investigators list.
25 March 2014	- Modification of the coordinating investigator's contact details - Rephrasing of the primary objective - Addition of a secondary objective - Modifications of inclusion and non-inclusion criteria (precision on IC N°9, modification of NIC N°1 of the selection process, and modification of IC N°2, ICN°6, NIC N°3 and NIC N°6 of the randomization process). - Clarification on the population considered for the analysis of the primary endpoint - Precision on the duration of the cycle in figure 1 of the diagram of the study - Clarification on cross-over between study arms A and B - Modification of the stratification factors - Clarification on non-randomisation reasons and treatment accountancy - Modifications of administration and dose reduction recommendations in the event of toxicity - Modifications of concomitant treatments, in the follow-up and exams. - Addition of explanatory diagram (general organization of the tumor sample circuit / period between the end of the induction treatment and randomization) - Planification of an interim analysis after the randomisation of 60 patients in the SAFIR02 program - Modifications of toxicities regarding eyes and skin - Clarification on SAEs criteria - Clarification on the moment of Steering Committee and IDMC meet - Modifications on biopsy collection - Correction of typographic errors
24 July 2014	- Modification of the investigators list.
07 January 2015	- Modifications of IC and NIC (modification of ICN°3 and NIC N°11 of the selection process) - Modification of Figure 1 - Update of the protocol (Tables 5 et 13, section 11.1.3) and investigator's brochures - Modification of section 7.7.2.4 (concomitant treatment administration) - Suppresssion of Section 10 (inclustion criteria previously listed) - Change of the CRB contact details - Modification of the stratification factors - Addition of an "other" category in Appendix 6 (Order of preference for treatment) - Clarification on Appendix 9 (Guidance on management of hepatotoxicity)
10 July 2015	- Modification of the investigators list
09 September 2015	- Modification of the study design with the addition of the substudy 2 to assess efficacy and toxicity of the antiPD-L1 MEDI4736 (Durvalumab). - Modification of IC and NIC (screening phase: IC N°7 and addition NIC N°3; Substudy 1: NIC N°6; NIC N°10; NIC N°12; NIC N°13). - Updates of the targeted therapies information. - Update of toxicity profiles of targeted therapies and toxicity management guidelines.
16 November 2015	- Modification of toxicity management of MEDI4736.

24 March 2016	- Modification study design and patients' diaries (Targeted therapy / Immunotherapy / Standard Chimiotherapy)
19 April 2016	- Modification of the investigators list
09 September 2016	- Increase of the number of patients included during screening phase. - Modification molecular analysis method with use of Formalin-Fixed Paraffin-Embedded tissue and plasma to generate tumoral genomic profile. - Modification of maintenance treatment with withdrawal of Erlotinib in epidermal cancers - Introduction of MEDI4736 pseudo-progression management guidelines.
16 November 2016	- Modification of the investigators list
16 January 2017	- Modification of the investigators list
22 March 2017	- Modification of the investigators list
19 September 2018	- Replacement of Dr Claire LETHROSNE by Dr Laetitia RAJPAR as a principal investigator at the hospital Louis Pasteur at Chartres. - Modification of the investigators list
25 March 2019	- Ending of AZD8931 manufacture - Futility analyses - Addition of targeted therapies (Olaparib, Savolitinib, Cobimetinib, and Vemurafenib) - Reduction of the number of tumoral assessment following 6 months treatment - Update of the Durvalumab investigator's brochure - Update of the Selumetinib investigator's brochure - Update of the AZD2014 investigator's brochure - Update of the AZD5363 investigator's brochure - Addition of a place of release of treatment batches - Addition of the possibility to use cytoblocks - Extension of durvalumab administrations until progression - Change of coordinator
04 June 2019	- Recruitment stopped - Addition of a storage site, releases and deliveries of experimental products - Update of the Olaparib investigator's brochure - Update of the Savolitinib investigator's brochure - Update of the AZD5363 investigator's brochure - Update of the Durvalumab investigator's brochure - General Data Protection Regulation integration - Modification of the investigators list
01 May 2020	- Update of the Olaparib investigator's brochure - Update of the Durvalumab investigator's brochure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported