Clinical trial results:
High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

Summary

EudraCT number	2012-000620-17
Trial protocol	DE DK NO IT
Global end of trial date	25 February 2022

Results information

Result version number	v2 (current)
This version publication date	28 March 2024
First version publication date	22 February 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	DRKS00005503

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02531841
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: 00005503

Notes:

Sponsors

Sponsor organisation name	Klinikum Der Landeshauptstadt Stuttgart gKAöR
Sponsor organisation address	Kriegsbergstrasse 60, Stuttgart, Germany, 70174
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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	18 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2022
Global end of trial reached?	Yes
Global end of trial date	25 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy measured as progression-free survival (PFS) of intensive chemotherapy followed by autologous stem-cell transplantation compared to conventional chemotherapy

Protection of trial subjects:

Interim analyses regarding safety issues were performed regularly in order to inform the Data Monitoring Committee (DMC). The underlying principles for the DMC are the patients' ethical and safety aspects. It is the task of the DMC to examine whether the
study’s conduct is still ethically justifiable, whether security of the patients is ensured and whether the study’s conduct is acceptable. Data on the patient's vital signs were taken at screening and all subsequent visits. The patient was free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Germany: 284
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	346
EEA total number of subjects	345

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)	262
From 65 to 84 years	84
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	346
Number of subjects completed	346

Period 1

Period 1 title	Induction treatment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Single arm treatment period

Arms

Arm title	Induction treatment

Arm description:

4 cycles (every 3 weeks), stem-cell harvest after 2nd cycle:
- Rituximab 375 mg/m²/d i.v. (days 0, 5)
- MTX 3.5 g/m² i.v. (day 1)
- Ara-C 2 x 2 g/m²/d i.v. (days 2-3)
- Thiotepa 30 mg/m2 i.v. (day 4)

Arm type	Induction treatment
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 10 mg/mL (referred to concentrate)
Dose: 3000 mg/m2 (total), for induction treatment and consolidation treatment

For induction treatment: 375 mg/m²/d i.v. (day 0, 5)

Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	TEPADINA® 100 mg
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)
Dose: 30 mg/kg (total),

For induction treatment: 30 mg/m2 i.v. (day 4)

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	ARA-cell® 4000 mg Infusionslösung
Pharmaceutical forms	Solution for infusion

Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 50 mg/mL
Dose: 32 g/m2 (total)

For induction treatment: 2 x 2 g/m²/d i.v. (days 2-3)

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Methotrexat HC 1000 mg Lösung Medac
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 100 mg/mL MTX (referred to concentrate)
Dose: 14 g/m2 (total), for induction treatment

For induction treatment: 3.5 g/m² i.v. (day 1)

Number of subjects in period 1	Induction treatment
Started	346
Completed	230
Not completed	116
incl. insufficient bone marrow recovery	15
Toxicity, AE/SAE	56
Wish of patient	5
Protocol deviation	40

Period 2

Period 2 title	Consolidation treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R-DeVIC

Arm description:

2 cycles of R-DeVIC (every 3 weeks):
- Rituximab 375 mg/m²/d i.v. (d 0)
- Dexamethasone 40 mg/d i.v. (d 1-3)
- Etoposide 100 mg/m²/d i.v. (d 1-3)
- Ifosfamide 1500 mg/m²/d i.v. (d 1-3)
- Carboplatin 300 mg/m² i.v. (d 1)

Arm type	Active comparator

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	ARA-cell® 4000 mg Infusionslösung
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 50 mg/mL
Dose: 32 g/m2 (total), for induction treatment

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Methotrexat HC 1000 mg Lösung Medac
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 100 mg/mL MTX (referred to concentrate)
Dose: 14 g/m2 (total), for induction treatment

Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	TEPADINA® 100 mg
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)
Dose: 30 mg/kg (total), for induction treatment, 20 mg/kg (total), for high-dose consolidation

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 10 mg/mL (referred to concentrate)
Dose: 3000 mg/m2 (total), for induction treatment and consolidation treatment

For consolidation treatment: 375 mg/m² i.v. (day 0)

Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	Busilvex®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 6 mg/mL (refers to concentrate)
Dose: 6.4 mg/ml (total)

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Fortecortin® Inject 40 mg
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection

Dosage and administration details:

Strength: 8,744 mg/ml Dexamethason-21-dihydrogen phosphate disodium (= 8 mg/ml dexamethasone)
Dose: 240 mg (total), for consolidation Arm A

Investigational medicinal product name	Etoposide/VP-16
Investigational medicinal product code	
Other name	ETOPOPHOS® 1000 mg
Pharmaceutical forms	Powder for solution for infusion

Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 11,4 mg/mL Etoposide phosphate (= 10 mg/mL Etoposide, referred to concentrate)
Dose: 600 mg/m2 (total), for consolidation Arm A

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	IFO-cell® 5 g
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 200 mg/mL
Dose: 9000 mg/m2 (total), for consolidation Arm A

Investigational medicinal product name	Carmustine/BCNU
Investigational medicinal product code	
Other name	CARMUBRIS®
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 3.3 mg/mL (refers to concentrate)
Dose: 400 mg/m2 (total), for consolidation in experimental intervention

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	CARBO-cell® 10 mg/mL Infusionslösung
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Strength: 10 mg/mL
Dose: 600 mg/m2 (total), for consolidation Arm A

Arm title	HDT-ASCT

Arm description:

High-dose chemotherapy (HDT):
- BCNU* 400 mg/m² i.v. (d -6)
- Thiotepa 2 x 5 mg/kg/d i.v. (d -5-(-4))
- ASCT (d 0)
* if not available at study site, Busulfan could have been administered: Busulfan 3.2 mg/kg/d i.v. (d -8-(-7))

Arm type	Experimental
Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	TEPADINA® 100 mg
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)
Dose: 30 mg/kg (total),
For consolidation treatment: 2 x 5 mg/kg/d i.v. (d -5-(-4))

Investigational medicinal product name	Carmustine/BCNU
Investigational medicinal product code	
Other name	CARMUBRIS®
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 3.3 mg/mL (refers to concentrate)
Dose: 400 mg/m2 (total).
For consolidation treatment: BCNU 400 mg/m² i.v. (d -6). If not available at study site, Busulfan could

have been administered:
Busulfan 3.2 mg/kg/d i.v. (d -8-(-7))

Number of subjects in period 2	R-DeVIC	HDT-ASCT
Started	115	115
Completed	115	114
Not completed	0	1
Major I/E violation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Induction treatment

Reporting group description: -

Reporting group values	Induction treatment	Total	
Number of subjects	346	346	
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)	262	262	
From 65-84 years	84	84	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	57.8		
standard deviation	± 9.5	-	
Gender categorical Units: Subjects			
Female	150	150	
Male	196	196	

End points

End points reporting groups

Reporting group title	Induction treatment
Reporting group description:	
4 cycles (every 3 weeks), stem-cell harvest after 2nd cycle: - Rituximab 375 mg/m²/d i.v. (days 0, 5) - MTX 3.5 g/m² i.v. (day 1) - Ara-C 2 x 2 g/m²/d i.v. (days 2-3) - Thiotepa 30 mg/m2 i.v. (day 4)	

Reporting group title	R-DeVIC
Reporting group description:	
2 cycles of R-DeVIC (every 3 weeks): - Rituximab 375 mg/m²/d i.v. (d 0) - Dexamethasone 40 mg/d i.v. (d 1-3) - Etoposide 100 mg/m²/d i.v. (d 1-3) - Ifosfamide 1500 mg/m²/d i.v. (d 1-3) - Carboplatin 300 mg/m² i.v. (d 1)	

Reporting group title	HDT-ASCT
Reporting group description:	
High-dose chemotherapy (HDT): - BCNU* 400 mg/m² i.v. (d -6) - Thiotepa 2 x 5 mg/kg/d i.v. (d -5-(-4)) - ASCT (d 0) * if not available at study site, Busulfan could have been administered: Busulfan 3.2 mg/kg/d i.v. (d -8-(-7))	

Primary: Progression-free survival (FAS)

End point title	Progression-free survival (FAS)
End point description:	

End point type	Primary
End point timeframe:	
Time from randomization until disease progression), disease relapse after achieving complete response (CR), or death from any cause.	

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Rate				
number (confidence interval 95%)				
6 months	0.83 (0.74 to 0.88)	0.83 (0.75 to 0.89)		
12 months	0.71 (0.62 to 0.78)	0.83 (0.74 to 0.88)		
24 months	0.61 (0.51 to 0.69)	0.79 (0.70 to 0.85)		
36 months	0.51 (0.41 to 0.60)	0.78 (0.69 to 0.85)		
48 months	0.50 (0.40 to 0.59)	0.77 (0.67 to 0.83)		

60 months	0.46 (0.35 to 0.56)	0.74 (0.62 to 0.82)		

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

The primary endpoint PFS was analyzed with a Cox proportional hazards model, containing the randomized treatment as hypothesis variable and the stratification variable response status as a covariate.

Comparison groups	R-DeVIC v HDT-ASCT
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0003
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.68

Secondary: Overall survival (FAS)

End point title	Overall survival (FAS)

End point description:

End point type	Secondary

End point timeframe:

Time from randomization until death from any cause.

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Rate				
number (confidence interval 95%)				
6 months	0.96 (0.90 to 0.98)	0.93 (0.86 to 0.96)		
12 months	0.89 (0.81 to 0.93)	0.91 (0.84 to 0.95)		
24 months	0.80 (0.72 to 0.87)	0.87 (0.79 to 0.92)		

36 months	0.71 (0.61 to 0.78)	0.86 (0.78 to 0.91)		
48 months	0.68 (0.58 to 0.76)	0.84 (0.76 to 0.90)		
60 months	0.63 (0.52 to 0.73)	0.84 (0.76 to 0.90)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	R-DeVIC v HDT-ASCT
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.81

Secondary: Relapse rate

End point title	Relapse rate
End point description:	
End point type	Secondary
End point timeframe:	
Time from randomization	

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Rate				
number (confidence interval 95%)				
6 months	0.1667 (0.1048 to 0.2409)	0.1316 (0.0772 to 0.2008)		
12 months	0.2725 (0.1940 to 0.3567)	0.1404 (0.0839 to 0.2109)		
24 months	0.3736 (0.2842 to 0.4629)	0.1770 (0.1129 to 0.2530)		
36 months	0.4494 (0.3519 to 0.5419)	0.1864 (0.1204 to 0.2636)		

48 months	0.4636 (0.3640 to 0.5572)	0.1994 (0.1300 to 0.2796)		
60 months	0.4820 (0.3784 to 0.5782)	0.2300 (0.1433 to 0.3289)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: 1 year follow-up

End point title	Quality of life EORTC QLQ-C30: 1 year follow-up

End point description:

End point type	Secondary

End point timeframe:

1 year follow up

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Points				
arithmetic mean (standard deviation)				
1 year follow-up	63.6 (± 20.1)	64.9 (± 20.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Non Relapse Mortality (FAS)

End point title	Non Relapse Mortality (FAS)

End point description:

End point type	Secondary

End point timeframe:

Time from randomization to death without prior relapse / disease progression

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Rate				
number (confidence interval 95%)				
6 months	0.0088 (0.0008 to 0.0437)	0.0351 (0.0114 to 0.0813)		
12 months	0.0175 (0.0034 to 0.0565)	0.0351 (0.0114 to 0.0813)		
24 months	0.0175 (0.0034 to 0.0565)	0.0351 (0.0114 to 0.0813)		
36 months	0.0386 (0.0124 to 0.0896)	0.0351 (0.0114 to 0.0813)		
48 months	0.0386 (0.0124 to 0.0896)	0.0351 (0.0114 to 0.0813)		
60 months	0.0626 (0.0200 to 0.1404)	0.0351 (0.0114 to 0.0813)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: 1 year follow-up: change from screening

End point title	Quality of life EORTC QLQ-C30: 1 year follow-up: change from screening

End point description:

Only patients with paired values before and after therapy were considered.

End point type	Secondary

End point timeframe:

From screening to 1 year follow up

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Points				
arithmetic mean (standard deviation)				
1 year follow-up: change from screening	11.0 (± 30.1)	14.8 (± 27.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: EOT change from screening	
End point title	Quality of life EORTC QLQ-C30: EOT change from screening
End point description: Only patients with paired values before and after therapy were considered	
End point type	Secondary
End point timeframe: From screening to end of treatment	

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Points				
arithmetic mean (standard deviation)				
Change from screening to end of treatment	6.9 (± 31.4)	8.3 (± 29.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: Screening	
End point title	Quality of life EORTC QLQ-C30: Screening
End point description:	
End point type	Secondary
End point timeframe: at screening	

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Points				
arithmetic mean (standard deviation)				
Screening	49.8 (± 26.1)	47.1 (± 27.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: Response assessment II

End point title	Quality of life EORTC QLQ-C30: Response assessment II

End point description:

End point type	Secondary

End point timeframe:

Response assessment II

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Points				
arithmetic mean (standard deviation)				
Response assessment II	55.0 (± 21.6)	57.5 (± 19.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: EOT

End point title	Quality of life EORTC QLQ-C30: EOT

End point description:

End point type	Secondary

End point timeframe:

End of treatment

End point values	R-DeVIC	HDT-ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Points				
arithmetic mean (standard deviation)				
End of treatment	57.7 (± 20.9)	53.1 (± 51.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Complete study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Arm A (R-DeVic)
Reporting group description: -	
Reporting group title	Induction therapy
Reporting group description: -	
Reporting group title	Arm B (HDT-ASCT)
Reporting group description: -	

Serious adverse events	Arm A (R-DeVic)	Induction therapy	Arm B (HDT-ASCT)
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 108 (23.15%)	200 / 346 (57.80%)	29 / 111 (26.13%)
number of deaths (all causes)	36	63	17
number of deaths resulting from adverse events	2	18	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	2 / 108 (1.85%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Jugular vein thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Mucosal inflammation			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pyrexia			
subjects affected / exposed	0 / 108 (0.00%)	11 / 346 (3.18%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	6 / 11	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Epistaxis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Hypercapnia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Interstitial lung disease			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Lung infiltration			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pneumonitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pneumothorax			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory arrest			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Respiratory failure			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Depression			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Self-injurious ideation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Suicide attempt			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemotherapeutic drug level increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
C-reactive protein increased			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Platelet count decreased			

subjects affected / exposed	2 / 108 (1.85%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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			
Brain herniation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Haemolytic transfusion reaction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Seroma			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Transplant failure			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Cardiac arrest			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Cerebral infarction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Cerebellar syndrome			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Epilepsy			

subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Hydrocephalus			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Hypoaesthesia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
IIIrd nerve paralysis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Meningism			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Neurotoxicity			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Seizure			

subjects affected / exposed	1 / 108 (0.93%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hygroma			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Syncope			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 108 (2.78%)	8 / 346 (2.31%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	3 / 3	7 / 8	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Cytopenia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (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	3 / 108 (2.78%)	45 / 346 (13.01%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	3 / 3	55 / 57	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 108 (1.85%)	11 / 346 (3.18%)	3 / 111 (2.70%)
occurrences causally related to treatment / all	2 / 2	17 / 17	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	4 / 108 (3.70%)	13 / 346 (3.76%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	4 / 4	13 / 14	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Diverticular perforation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Duodenal ulcer			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Large intestine perforation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pancreatitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Proctitis ulcerative			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Stomatitis			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Vomiting			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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			
Hepatotoxicity			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder rupture			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 108 (0.00%)	12 / 346 (3.47%)	4 / 111 (3.60%)
occurrences causally related to treatment / all	0 / 0	11 / 12	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 108 (0.00%)	4 / 346 (1.16%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular disorder			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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

Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
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 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Back pain			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Abscess jaw			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Arthritis bacterial			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Brain abscess			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Bronchitis			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (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
Atypical pneumonia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterial infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Candida sepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Cerebral candidiasis			

subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Device related sepsis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 108 (0.93%)	5 / 346 (1.45%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 108 (0.00%)	4 / 346 (1.16%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Escherichia bacteraemia			

subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Endocarditis staphylococcal			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Empyema			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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 infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
H1N1 influenza			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Herpes zoster infection neurological			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Infection			
subjects affected / exposed	0 / 108 (0.00%)	7 / 346 (2.02%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	5 / 8	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Klebsiella infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Mucormycosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Medical device site infection			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (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
Necrotising soft tissue infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Neutropenic infection			
subjects affected / exposed	1 / 108 (0.93%)	8 / 346 (2.31%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	7 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	3 / 111 (2.70%)
occurrences causally related to treatment / all	0 / 0	5 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Osteomyelitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Osteomyelitis bacterial			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Peritonitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pneumonia			
subjects affected / exposed	2 / 108 (1.85%)	24 / 346 (6.94%)	4 / 111 (3.60%)
occurrences causally related to treatment / all	1 / 2	20 / 26	3 / 4
deaths causally related to treatment / all	0 / 0	4 / 4	2 / 2
Pneumonia necrotising			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pneumonia escherichia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pneumonia fungal			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumonia influenzal			

subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Post procedural infection			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Rectal abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Puncture site abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pyelonephritis			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Pseudomonal sepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Sepsis			
subjects affected / exposed	0 / 108 (0.00%)	18 / 346 (5.20%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	12 / 19	2 / 2
deaths causally related to treatment / all	0 / 0	3 / 3	1 / 1
Septic shock			
subjects affected / exposed	0 / 108 (0.00%)	8 / 346 (2.31%)	3 / 111 (2.70%)
occurrences causally related to treatment / all	0 / 0	7 / 9	3 / 3
deaths causally related to treatment / all	0 / 0	3 / 3	0 / 0
Skin infection			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (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
Urinary tract infection			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Urosepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Viral infection			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (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
Wound infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Wound abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Gout			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Hyperkalaemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (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
Hypernatraemia			

subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A (R-DeVic)	Induction therapy	Arm B (HDT-ASCT)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 108 (100.00%)	344 / 346 (99.42%)	111 / 111 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Prostate cancer			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Embolism			
subjects affected / exposed	3 / 108 (2.78%)	31 / 346 (8.96%)	2 / 111 (1.80%)
occurrences (all)	3	31	2
Flushing			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences (all)	0	1	1

Haematoma			
subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	0 / 111 (0.00%)
occurrences (all)	0	5	0
Hypertension			
subjects affected / exposed	17 / 108 (15.74%)	94 / 346 (27.17%)	28 / 111 (25.23%)
occurrences (all)	17	94	28
Hypotension			
subjects affected / exposed	7 / 108 (6.48%)	48 / 346 (13.87%)	15 / 111 (13.51%)
occurrences (all)	7	50	15
Jugular vein thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 108 (0.00%)	10 / 346 (2.89%)	2 / 111 (1.80%)
occurrences (all)	0	10	2
Subclavian vein thrombosis			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	1	1	0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Superficial vein thrombosis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Lung lobectomy			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Tooth extraction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Device related thrombosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Fatigue			
subjects affected / exposed	25 / 108 (23.15%)	110 / 346 (31.79%)	37 / 111 (33.33%)
occurrences (all)	25	112	37
Gait disturbance			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Impaired healing			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Infusion site extravasation			
subjects affected / exposed	2 / 108 (1.85%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	2	1	0
Injection site haematoma			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Injection site haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0

Localised oedema			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Mucosal inflammation			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences (all)	1	1	1
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Oedema			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	19 / 108 (17.59%)	106 / 346 (30.64%)	21 / 111 (18.92%)
occurrences (all)	19	108	21
Pain			
subjects affected / exposed	14 / 108 (12.96%)	119 / 346 (34.39%)	25 / 111 (22.52%)
occurrences (all)	14	120	25
Pyrexia			
subjects affected / exposed	10 / 108 (9.26%)	164 / 346 (47.40%)	49 / 111 (44.14%)
occurrences (all)	10	169	49
Swelling face			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 108 (0.93%)	32 / 346 (9.25%)	11 / 111 (9.91%)
occurrences (all)	1	32	11
Reproductive system and breast disorders			
Penis disorder			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences (all)	0	1	1

Asthma			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Atelectasis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 108 (0.00%)	7 / 346 (2.02%)	3 / 111 (2.70%)
occurrences (all)	0	7	3
Epistaxis			
subjects affected / exposed	6 / 108 (5.56%)	67 / 346 (19.36%)	10 / 111 (9.01%)
occurrences (all)	6	68	10
Dyspnoea			
subjects affected / exposed	4 / 108 (3.70%)	55 / 346 (15.90%)	8 / 111 (7.21%)
occurrences (all)	4	55	8
Hiccups			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	2 / 111 (1.80%)
occurrences (all)	0	2	2
Hypoxia			
subjects affected / exposed	0 / 108 (0.00%)	11 / 346 (3.18%)	1 / 111 (0.90%)
occurrences (all)	0	11	1
Lung diffusion disorder			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 108 (0.00%)	4 / 346 (1.16%)	2 / 111 (1.80%)
occurrences (all)	0	4	2
Pleural effusion			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	2 / 111 (1.80%)
occurrences (all)	0	2	2
Pneumothorax			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0

Pulmonary haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Respiratory failure			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	1 / 111 (0.90%)
occurrences (all)	0	5	1
Anxiety			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	4	0
Confusional state			
subjects affected / exposed	9 / 108 (8.33%)	83 / 346 (23.99%)	17 / 111 (15.32%)
occurrences (all)	9	83	17
Depressed mood			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	13 / 108 (12.04%)	45 / 346 (13.01%)	10 / 111 (9.01%)
occurrences (all)	13	45	10
Hallucination			
subjects affected / exposed	1 / 108 (0.93%)	11 / 346 (3.18%)	6 / 111 (5.41%)
occurrences (all)	1	11	6
Insomnia			
subjects affected / exposed	7 / 108 (6.48%)	31 / 346 (8.96%)	6 / 111 (5.41%)
occurrences (all)	8	31	6
Mania			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Panic attack			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Suicidal ideation			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	47 / 108 (43.52%)	280 / 346 (80.92%)	50 / 111 (45.05%)
occurrences (all)	47	281	50
Aspartate aminotransferase increased			
subjects affected / exposed	26 / 108 (24.07%)	230 / 346 (66.47%)	48 / 111 (43.24%)
occurrences (all)	26	232	48
Blood alkaline phosphatase abnormal			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Blood bilirubin increased			
subjects affected / exposed	8 / 108 (7.41%)	119 / 346 (34.39%)	18 / 111 (16.22%)
occurrences (all)	8	119	18
Blood creatinine increased			
subjects affected / exposed	21 / 108 (19.44%)	134 / 346 (38.73%)	24 / 111 (21.62%)
occurrences (all)	21	137	24
Blood culture positive			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	4	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram T wave inversion			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	2 / 111 (1.80%)
occurrences (all)	0	3	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	51 / 108 (47.22%)	230 / 346 (66.47%)	71 / 111 (63.96%)
occurrences (all)	51	232	71
Platelet count decreased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Weight increased			
subjects affected / exposed	2 / 108 (1.85%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	2	2	0
Weight decreased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	0 / 108 (0.00%)	12 / 346 (3.47%)	0 / 111 (0.00%)
occurrences (all)	0	13	0
Infusion related reaction			
subjects affected / exposed	1 / 108 (0.93%)	16 / 346 (4.62%)	12 / 111 (10.81%)
occurrences (all)	1	16	12
Procedural pneumothorax			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Transfusion reaction			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Bradycardia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	2 / 108 (1.85%)	12 / 346 (3.47%)	5 / 111 (4.50%)
occurrences (all)	2	13	6
Palpitations			
subjects affected / exposed	1 / 108 (0.93%)	9 / 346 (2.60%)	1 / 111 (0.90%)
occurrences (all)	1	9	1
Sinus bradycardia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	1 / 111 (0.90%)
occurrences (all)	0	2	2
Sinus node dysfunction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	2 / 111 (1.80%)
occurrences (all)	0	0	2
Tachycardia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	1 / 111 (0.90%)
occurrences (all)	0	2	1
Ventricular arrhythmia			
subjects affected / exposed	0 / 108 (0.00%)	7 / 346 (2.02%)	2 / 111 (1.80%)
occurrences (all)	0	7	2
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Cognitive disorder			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 108 (0.00%)	11 / 346 (3.18%)	3 / 111 (2.70%)
occurrences (all)	0	13	3
Dizziness postural			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Dysaesthesia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Dysarthria			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Encephalopathy			
subjects affected / exposed	2 / 108 (1.85%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	14 / 108 (12.96%)	100 / 346 (28.90%)	14 / 111 (12.61%)
occurrences (all)	14	100	14
Hemiplegia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Horner's syndrome			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Leukoencephalopathy			
subjects affected / exposed	1 / 108 (0.93%)	3 / 346 (0.87%)	2 / 111 (1.80%)
occurrences (all)	1	3	2
Loss of consciousness			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Memory impairment			

subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Motor dysfunction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Orthostatic intolerance			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	6 / 108 (5.56%)	26 / 346 (7.51%)	3 / 111 (2.70%)
occurrences (all)	6	26	3
Parkinsonism			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Partial seizures			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Peripheral motor neuropathy			
subjects affected / exposed	3 / 108 (2.78%)	15 / 346 (4.34%)	1 / 111 (0.90%)
occurrences (all)	3	15	1
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 108 (6.48%)	17 / 346 (4.91%)	1 / 111 (0.90%)
occurrences (all)	7	17	1
Quadriparesis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	1 / 108 (0.93%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	1	3	0
Somnolence			
subjects affected / exposed	5 / 108 (4.63%)	19 / 346 (5.49%)	5 / 111 (4.50%)
occurrences (all)	5	19	5
Syncope			
subjects affected / exposed	3 / 108 (2.78%)	17 / 346 (4.91%)	3 / 111 (2.70%)
occurrences (all)	4	17	3
Tremor			

subjects affected / exposed	1 / 108 (0.93%)	5 / 346 (1.45%)	1 / 111 (0.90%)
occurrences (all)	1	5	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	102 / 108 (94.44%)	330 / 346 (95.38%)	103 / 111 (92.79%)
occurrences (all)	102	336	103
Febrile neutropenia			
subjects affected / exposed	14 / 108 (12.96%)	176 / 346 (50.87%)	67 / 111 (60.36%)
occurrences (all)	14	182	67
Haemolysis			
subjects affected / exposed	3 / 108 (2.78%)	6 / 346 (1.73%)	3 / 111 (2.70%)
occurrences (all)	3	6	3
Leukopenia			
subjects affected / exposed	89 / 108 (82.41%)	313 / 346 (90.46%)	101 / 111 (90.99%)
occurrences (all)	89	313	101
Lymphadenopathy			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Neutropenia			
subjects affected / exposed	74 / 108 (68.52%)	260 / 346 (75.14%)	85 / 111 (76.58%)
occurrences (all)	74	261	85
Lymphopenia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	101 / 108 (93.52%)	330 / 346 (95.38%)	108 / 111 (97.30%)
occurrences (all)	102	334	109
Thrombocytosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Hypoacusis			

subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Tinnitus			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	0 / 111 (0.00%)
occurrences (all)	0	5	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Diplopia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Eye haematoma			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Retinal haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Swelling of eyelid			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	1 / 111 (0.90%)
occurrences (all)	0	3	1

Visual acuity reduced			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Visual field defect			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Visual impairment			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Vitreous haemorrhage			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 108 (5.56%)	56 / 346 (16.18%)	23 / 111 (20.72%)
occurrences (all)	6	56	23
Ascites			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	1 / 111 (0.90%)
occurrences (all)	0	3	1
Aphthous ulcer			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Anal ulcer			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Anal fissure			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	12 / 108 (11.11%)	74 / 346 (21.39%)	9 / 111 (8.11%)
occurrences (all)	13	74	9
Diarrhoea			

subjects affected / exposed	7 / 108 (6.48%)	67 / 346 (19.36%)	65 / 111 (58.56%)
occurrences (all)	7	69	65
Dental caries			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	2 / 111 (1.80%)
occurrences (all)	0	1	2
Dysphagia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences (all)	0	1	1
Gastritis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	2 / 111 (1.80%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 108 (1.85%)	14 / 346 (4.05%)	3 / 111 (2.70%)
occurrences (all)	2	14	3
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	18 / 346 (5.20%)	0 / 111 (0.00%)
occurrences (all)	0	18	0
Haemorrhoids			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Ileus			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	23 / 108 (21.30%)	113 / 346 (32.66%)	63 / 111 (56.76%)
occurrences (all)	23	114	63
Oesophagitis			
subjects affected / exposed	1 / 108 (0.93%)	6 / 346 (1.73%)	5 / 111 (4.50%)
occurrences (all)	1	6	5
Palatal disorder			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Rectal ulcer			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Salivary gland calculus			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Proctalgia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	10 / 108 (9.26%)	115 / 346 (33.24%)	87 / 111 (78.38%)
occurrences (all)	10	118	87
Tongue haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Tooth disorder			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	9 / 108 (8.33%)	50 / 346 (14.45%)	44 / 111 (39.64%)
occurrences (all)	9	50	44
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0

Hepatic failure			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	4	0
Hepatic steatosis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	38 / 108 (35.19%)	144 / 346 (41.62%)	49 / 111 (44.14%)
occurrences (all)	38	144	49
Acne			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Decubitus ulcer			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Dermatitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Dermatitis bullous			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Epidermolysis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	1	0	1
Hyperhidrosis			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	1 / 108 (0.93%)	5 / 346 (1.45%)	0 / 111 (0.00%)
occurrences (all)	1	5	0
Pruritus			
subjects affected / exposed	2 / 108 (1.85%)	26 / 346 (7.51%)	6 / 111 (5.41%)
occurrences (all)	2	26	6
Rash			
subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	1 / 111 (0.90%)
occurrences (all)	0	7	2
Rash erythematous			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Solar lentigo			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	2 / 108 (1.85%)	27 / 346 (7.80%)	5 / 111 (4.50%)
occurrences (all)	2	27	5
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	1 / 111 (0.90%)
occurrences (all)	0	5	1
Chronic kidney disease			

subjects affected / exposed	0 / 108 (0.00%)	13 / 346 (3.76%)	2 / 111 (1.80%)
occurrences (all)	0	14	2
Haematuria			
subjects affected / exposed	2 / 108 (1.85%)	12 / 346 (3.47%)	4 / 111 (3.60%)
occurrences (all)	2	12	4
Nocturia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Pollakiuria			
subjects affected / exposed	1 / 108 (0.93%)	4 / 346 (1.16%)	0 / 111 (0.00%)
occurrences (all)	1	5	0
Urinary incontinence			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	1	1	0
Urinary retention			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Urethral haemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 108 (0.00%)	4 / 346 (1.16%)	0 / 111 (0.00%)
occurrences (all)	0	4	0
Hyperthyroidism			
subjects affected / exposed	0 / 108 (0.00%)	16 / 346 (4.62%)	1 / 111 (0.90%)
occurrences (all)	0	16	1
Hypothyroidism			
subjects affected / exposed	3 / 108 (2.78%)	17 / 346 (4.91%)	0 / 111 (0.00%)
occurrences (all)	3	17	0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Arthralgia			

subjects affected / exposed	0 / 108 (0.00%)	5 / 346 (1.45%)	0 / 111 (0.00%)
occurrences (all)	0	6	0
Back pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	4 / 108 (3.70%)	84 / 346 (24.28%)	5 / 111 (4.50%)
occurrences (all)	4	85	5
Exostosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Joint ankylosis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			
subjects affected / exposed	5 / 108 (4.63%)	25 / 346 (7.23%)	4 / 111 (3.60%)
occurrences (all)	5	25	4
Musculoskeletal stiffness			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 108 (0.93%)	8 / 346 (2.31%)	1 / 111 (0.90%)
occurrences (all)	1	8	1
Rhabdomyolysis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Sacroiliitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Sjogren's syndrome			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Soft tissue necrosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 108 (0.93%)	13 / 346 (3.76%)	8 / 111 (7.21%)
occurrences (all)	1	13	8
Acarodermatitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Atypical pneumonia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	6 / 108 (5.56%)	30 / 346 (8.67%)	4 / 111 (3.60%)
occurrences (all)	6	30	4
Cellulitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Clostridial infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	2 / 111 (1.80%)
occurrences (all)	0	1	2
Conjunctivitis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Cutaneous mucormycosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Cytomegalovirus infection reactivation			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	1 / 111 (0.90%)
occurrences (all)	0	1	1
Device related infection			
subjects affected / exposed	3 / 108 (2.78%)	53 / 346 (15.32%)	23 / 111 (20.72%)
occurrences (all)	3	55	23
Enterobacter sepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Erysipelas			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Escherichia bacteraemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Escherichia infection			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Escherichia sepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Encephalitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Enterococcal infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 108 (0.93%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	1	1	0
Eye infection			
subjects affected / exposed	3 / 108 (2.78%)	7 / 346 (2.02%)	0 / 111 (0.00%)
occurrences (all)	3	8	0
Folliculitis			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Fungal skin infection			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Hepatitis A			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Herpes simplex			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Herpes virus infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Human herpesvirus 6 infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 108 (0.00%)	4 / 346 (1.16%)	0 / 111 (0.00%)
occurrences (all)	0	4	0
Infection			
subjects affected / exposed	0 / 108 (0.00%)	6 / 346 (1.73%)	1 / 111 (0.90%)
occurrences (all)	0	6	1
Klebsiella bacteraemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Klebsiella infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Labyrinthitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Neutropenic sepsis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Meningitis viral			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Mucosal infection			
subjects affected / exposed	2 / 108 (1.85%)	42 / 346 (12.14%)	23 / 111 (20.72%)
occurrences (all)	2	42	23
Nasopharyngitis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Neutropenic infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Oesophageal candidiasis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Parotitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 108 (0.00%)	36 / 346 (10.40%)	5 / 111 (4.50%)
occurrences (all)	0	37	5
Parainfluenzae virus infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Proteus infection			

subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Pseudomonal sepsis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	2 / 108 (1.85%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	2	2	0
Skin infection			
subjects affected / exposed	5 / 108 (4.63%)	38 / 346 (10.98%)	4 / 111 (3.60%)
occurrences (all)	5	38	4
Soft tissue infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Staphylococcal infection			
subjects affected / exposed	0 / 108 (0.00%)	2 / 346 (0.58%)	0 / 111 (0.00%)
occurrences (all)	0	2	0
Staphylococcal sepsis			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 346 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	0	1
Tooth infection			

subjects affected / exposed	1 / 108 (0.93%)	10 / 346 (2.89%)	0 / 111 (0.00%)
occurrences (all)	1	10	0
Subcutaneous abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Systemic candida			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	9 / 108 (8.33%)	52 / 346 (15.03%)	14 / 111 (12.61%)
occurrences (all)	9	53	14
Urinary tract infection bacterial			
subjects affected / exposed	1 / 108 (0.93%)	0 / 346 (0.00%)	0 / 111 (0.00%)
occurrences (all)	1	0	0
Vascular device infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Vulval abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 108 (3.70%)	27 / 346 (7.80%)	8 / 111 (7.21%)
occurrences (all)	4	27	8
Dehydration			
subjects affected / exposed	2 / 108 (1.85%)	8 / 346 (2.31%)	0 / 111 (0.00%)
occurrences (all)	2	8	0
Diabetes mellitus			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Fluid overload			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	1 / 111 (0.90%)
occurrences (all)	0	4	1

Hyperglycaemia			
subjects affected / exposed	29 / 108 (26.85%)	152 / 346 (43.93%)	25 / 111 (22.52%)
occurrences (all)	29	154	25
Hyperkalaemia			
subjects affected / exposed	11 / 108 (10.19%)	71 / 346 (20.52%)	10 / 111 (9.01%)
occurrences (all)	11	71	10
Hypernatraemia			
subjects affected / exposed	0 / 108 (0.00%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	0	3	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	2 / 108 (1.85%)	3 / 346 (0.87%)	0 / 111 (0.00%)
occurrences (all)	2	3	0
Hypokalaemia			
subjects affected / exposed	3 / 108 (2.78%)	19 / 346 (5.49%)	5 / 111 (4.50%)
occurrences (all)	4	24	5
Hypomagnesaemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	20 / 108 (18.52%)	121 / 346 (34.97%)	29 / 111 (26.13%)
occurrences (all)	20	121	29
Hypophosphataemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 346 (0.29%)	0 / 111 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2018	Administrative changes: Change of principal investigator in center Hannover, Closure of study center Berlin (no recruitment), Registration of trial in ClinicalTrials.gov (NCT02531841) Clarification with reference to in-/exclusion criteria: • Addition of randomization criterion no. 4: "Exclusion criterion no. 6 not applicable for re-check for randomization" • Additional wording in randomization criterion no. 1: "Sufficient stem cell harvest (≥ 3 x 106 CD34+ cells/kg of body weight)" • Additional wording in exclusion criterion no. 6: "Only applicable for patient inclusion (registration) not applicable for re-check for randomization" • Correction of contents regarding the contraception time period of female and male patients on the basis of three SmPCs Sample size calculation: Increase of • recruitment period due to increase of number of patients enrolled • number of patients, that need to be recruited to obtain the originally planned number of 220 patients, that were to be randomized Adaption of figures and timelines: • Addition of specification "for evaluation of primary endpoint" regarding trial duration and time table Adaption of involved number of sites and countries: • Number of sites increased and the participating countries changed Adaption in flow chart: • Specification of response statement: "Whole brain MRI and response statement according to IPCG criteria" • More detailed timelines for RA III in case of postponement of consolidation therapy • Addition of more precise time period recommended for FU visits during year 3-5 and after year 5 Addition of special treatment recommendations regarding the Induction treatment phase. A special "pregnancy form", which must be used replaced the former so called "SAE reporting form". Detailed explanation was added regarding storage and use of stem cells. Improved wording regarding documentation and reporting of AEs and SAEs. Explanation regarding the handling of biomaterial was added.
14 June 2018	Additional demand of ethics committee to substantial amendment 01: Change in wording in Patient Informed Consent (PIC), version V03, section 12 regarding the notification of health damages which could have occurred as a result of the clinical study. Furthermore, a change in wording regarding documentation and reporting of AEs (section 10.1.2): "AEs must be documented … until day 60 after last administration of study medication randomization. If patient could not be randomized, AE documentation and reporting should be made until day 60 after last administration of study medication".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27098429