Clinical trial results:
Subcutaneous Rituximab and Intravenous Bendamustine in very Elderly Patients or Elderly Medically Non Fit Patients("slow go") with Aggressive CD-20-positive B-cell Lymphoma
Short tiltle: BRENDA

Summary

EudraCT number	2010-024004-98
Trial protocol	DE
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	06 August 2020
First version publication date	06 August 2020

Trial information

Trial identification

Sponsor protocol code	DSHNHL2010-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universitätsmedizin der Georg-August-Universität Göttingen
Sponsor organisation address	Robert-Koch-Straße 40, Göttingen, Germany, 37075
Public contact	Kristina Wilhelm, iOMEDICO AG, 0049 76115242523, kristina.wilhelm@iomedico.com
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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	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2018
Global end of trial reached?	Yes
Global end of trial date	02 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary aim is to determine the feasibility, toxicity and efficacy of RB in very elderly patients or elderly medically non fit patients As no standard treatment exists, a phase II trial is an appropriate approach to define safety and efficacy of rituximab and bendamustine. The evaluation of safety and toxicity includes the following:
Toxicity, graded according to NCI-CTC version 4.03.,
Adverse events,
Serious adverse events (SAE), and SUSAR
Protocol adherence
Efficacy is determined according to the 2 year-rate of progression-free-survival.
Secondary aims of this study are the determination of 2 year-rate of overall survival (OS), rate of complete (CR), partial remission (PR) and rate of primary progression (PRO), relapse rate, treatment-related deaths, 2 year-rate of event free survival EFS, safety, protocol adherence (according to 4.3.1.3) , ability for self-care and quality of life (QoL) assessed by a GA (geriatric assessment) and EORTC-QLQ-C30.

Protection of trial subjects:

The aim of the B-R-ENDA trial is to investigate efficacy and toxicity of the combination treatment of bendamustine and rituximab in old patients or in elderly patients with high comorbidity who do not qualify for a CHOP like treatment. However, most of the patients included in this clinical trial will die of disease progression within weeks of diagnosis.
As the RB-regimens is less toxic than the R-CHOP regimen in patients with follicular lymphoma, it can be expected to be safer for non-fit patients with DLBCL. As it demonstrated some activity in patients with recurrent or relapsed aggressive lymphoma, the use in first line treatment is justified. Safety analysis will be performed on a regular basis.
For the first patients treated in the main-phase of the study (patients 21 to 31), before signing the informed consent, the treating physicians has to check whether an inclusion of the patient is possible, as patient 21 to 31 will be included sequentially with a minimum of an one-week interval between each patient. In this phase of the trial, the centers will be informed by the sponsor regularly about the actual status of the study.

Background therapy:

The trial treatment started with a pre-phase treatment including one application of intravenous rituximab, followed by 3 cycles of rituximab and bendamustine (BR) every 3 weeks. Thereafter, patients were restaged based on the treatment response.

Evidence for comparator: -

Actual start date of recruitment	01 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	1
From 65 to 84 years	50
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

Patients with a newly diagnosed CD20+ aggressive lymphoma aged 81 years as well as patients aged 61 to 80 with comorbidities not qualifying for CHOP chemotherapy, regardless of gender or disease stage. PS-ECOG <4 with life expectancy of at least 6 weeks, when lymphoma is treated. 24 German recruiting hospitals between July 2012 and Feb. 2016.

Pre-assignment

Screening details:

For the Run-in phase, 21 patients screened with one screening failure.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	run-in and main phase

Arm description:

Run-in phase
Patients 1 to 20

Pre-phase:
Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m² body surface area IV d-3

Trial treatment:
Cycles 1 to 7: Rituximab 375 mg /m² body surface area IV day 1, every 3 weeks
Cycles 1 to 6: Bendamustine 90 mg /m² body surface area IV day 1 and 2 (or day 2 and 3 at investigators decision),
every 3 weeks

Main-Phase
Patients 21 up to the end of recruitment (after the analysis of the Safety Data by the DSMB for the first 20 patients and of the Rituximab SC Data available from ongoing studies at that timepoint). The first 10 patients of the main-phase will be recruited sequentially on a minimal weekly basis

Pre-phase:
Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m² body surface area IV d-3

Trial treatment:
Cycles 1 to 7: Rituximab SC 1400 mg absolute day 1, every 3 weeks
Cycles 1 to 6: Bendamustine 90 mg /m² body surface area IV
day 1 and 2 (or day 2 and 3 at investigators decision),
eve

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	LEVACT®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receiving bendamustine will be administered at a dose of 90 mg/m². The recommended infusion time is 30 to 60 minutes. The prepared bendamustine solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.

Investigational medicinal product name	Rituximab IV
Investigational medicinal product code	
Other name	Mabthera i.v.®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receiving rituximab IV will be administered a dose of 375 mg/m². The appropriate amount of solution should be withdrawn from the vial from the following calculation:
Volume (ml) = BSA (m²) * dose (375 mg/m²) / concentration of reconstituted solution mg/ml (100 mg/10 ml and/or 500 mg/50 ml)
The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent doses of rituximab IV can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minutes intervals, to a maximum of 400 mg/hour.
The prepared rituximab IV solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus

Investigational medicinal product name	Rituximab s.c.
Investigational medicinal product code	
Other name	MabThera SC, Rituxan SC
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Main-Phase
Patients 21 up to the end of recruitment (after the analysis of the Safety Data by the DSMB for the first 20 patients and of the Rituximab SC Data available from ongoing studies at that timepoint). The first 10 patients of the main-phase will be recruited sequentially on a minimal weekly basis

Pre-phase:
Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m² body surface area IVd-3

Trial treatment:
Cycles 1 to 7: Rituximab SC 1400 mg absolute day 1, every 3 weeks
Cycles 1 to 6: Bendamustine 90 mg /m² body surface area IV
day 1 and 2 (or day 2 and 3 at investigators decision),
every 3 weeks

G-CSF according to ASCO/ESMO guidelines

Number of subjects in period 1	run-in and main phase
Started	68
Completed	68

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

Patients 1 to 20

Pre-phase:
Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m2 body surface area IV d-3

Trial treatment:
Cycles 1 to 7: Rituximab 375 mg /m2 body surface area IV day 1, every 3 weeks
Cycles 1 to 6: Bendamustine 90 mg /m2 body surface area IV day 1 and 2 (or day 2 and 3 at investigators decision),
every 3 weeks

Main-Phase
Patients 21 to 68. The first 10 patients of the main-phase will be recruited sequentially on a minimal weekly basis

Pre-phase:
Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m² body surface area IV d-3

Trial treatment:
Cycles 1 to 7: Rituximab SC 1400 mg absolute day 1, every 3 weeks
Cycles 1 to 6: Bendamustine 90 mg /m² body surface area IV
day 1 and 2 (or day 2 and 3 at investigators decision),
every 3 weeks

G-CSF according to ASCO/ESMO guidelines

Reporting group values	overall trial	Total	
Number of subjects	68	68	
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	
From 65-84 years	50	50	
85 years and over	17	17	
Gender categorical Units: Subjects			
Female	46	46	
Male	22	22	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: all registered patients	
Subject analysis set title	FAS-I
Subject analysis set type	Full analysis
Subject analysis set description: patients > 80 years	
Subject analysis set title	FAS-II
Subject analysis set type	Full analysis

Subject analysis set description:

patients 61 - 80 years

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from FAS with fulfilled inclusion criteria and reference pathology according to protocol and at least on dose Rituximab and/or Bendamustine.

Subject analysis set title	PPS-I
Subject analysis set type	Per protocol

Subject analysis set description:

patients > 80 years

Subject analysis set title	PPS-II
Subject analysis set type	Per protocol

Subject analysis set description:

patients 61 - 80 years

Reporting group values	Full Analysis Set (FAS)	FAS-I	FAS-II
Number of subjects	68	39	29
Age categorical Units: Subjects			
Adults (18-64 years)	1	0	1
From 65-84 years	50	22	28
85 years and over	17	17	0
Gender categorical Units: Subjects			
Female	46	28	18
Male	22	11	11

Reporting group values	Per Protocol Set (PPS)	PPS-I	PPS-II
Number of subjects	57	34	23
Age categorical Units: Subjects			
Adults (18-64 years)	1	0	1
From 65-84 years	40	18	22
85 years and over	16	16	0
Gender categorical Units: Subjects			
Female	38	24	14
Male	19	10	9

End points

End points reporting groups

Reporting group title	run-in and main phase
Reporting group description:	
Run-in phase Patients 1 to 20 Pre-phase: Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m² body surface area IV d-3 Trial treatment: Cycles 1 to 7: Rituximab 375 mg /m² body surface area IV day 1, every 3 weeks Cycles 1 to 6: Bendamustine 90 mg /m² body surface area IV day 1 and 2 (or day 2 and 3 at investigators decision), every 3 weeks Main-Phase Patients 21 up to the end of recruitment (after the analysis of the Safety Data by the DSMB for the first 20 patients and of the Rituximab SC Data available from ongoing studies at that timepoint). The first 10 patients of the main-phase will be recruited sequentially on a minimal weekly basis Pre-phase: Prednisolone 100 mg absolute p.o. day -7 to -1 Rituximab 375 mg/m² body surface area IV d-3 Trial treatment: Cycles 1 to 7: Rituximab SC 1400 mg absolute day 1, every 3 weeks Cycles 1 to 6: Bendamustine 90 mg /m² body surface area IV day 1 and 2 (or day 2 and 3 at investigators decision), eve	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: all registered patients	
Subject analysis set title	FAS-I
Subject analysis set type	Full analysis
Subject analysis set description: patients > 80 years	
Subject analysis set title	FAS-II
Subject analysis set type	Full analysis
Subject analysis set description: patients 61 - 80 years	
Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description: All patients from FAS with fulfilled inclusion criteria and reference pathology according to protocol and at least on dose Rituximab and/or Bendamustine.	
Subject analysis set title	PPS-I
Subject analysis set type	Per protocol
Subject analysis set description: patients > 80 years	
Subject analysis set title	PPS-II
Subject analysis set type	Per protocol
Subject analysis set description: patients 61 - 80 years	

Primary: 2 years progression-free survival

End point title	2 years progression-free survival

End point description:

End point type	Primary

End point timeframe:

until 2 years after end-of-treatment

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	29	18	11

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	23	16	7	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Primary: therapy-associated deaths

End point title	therapy-associated deaths

End point description:

End point type	Primary

End point timeframe:

until end-of-study

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	10	5	5

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	9	4	5	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Primary: frequency of grade 3 to 5 adverse events and SAEs

End point title	frequency of grade 3 to 5 adverse events and SAEs
End point description:	
End point type	Primary
End point timeframe: until end of study	

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number	68	137	76	61

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Primary: adherence to the protocol

End point title	adherence to the protocol

End point description:

End point type	Primary

End point timeframe:
until end-of-treatment

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	33	22	11

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Secondary: 2 years overall survival (OS)

End point title	2 years overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:
until end-of-trial

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	33	20	13

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	25	17	8	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Secondary: event-free-survival (EFS)

End point title	event-free-survival (EFS)
End point description:	
End point type	Secondary
End point timeframe: until end-of-trial	

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	16	13	3

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	15	12	3	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Secondary: complete remission rate (CR)	
End point title	complete remission rate (CR)
End point description:	
End point type	Secondary
End point timeframe: until end-of-trial	

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	21	21	18	3

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	20	17	3	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Secondary: partial remission rate (PR)

End point title	partial remission rate (PR)

End point description:

End point type	Secondary

End point timeframe:

until end-of-study

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	7	2	5

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	5	2	3	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Secondary: rate of primary progression (PD)

End point title	rate of primary progression (PD)

End point description:

End point type	Secondary

End point timeframe:

until end-of-study

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	39	29
Units: number of patients	68	13	5	8

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	34	23	
Units: number of patients	9	3	6	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Secondary: relapse rate at end of therapy

End point title	relapse rate at end of therapy

End point description:

End point type	Secondary

End point timeframe:
until end-of-study

End point values	run-in and main phase	Full Analysis Set (FAS)	FAS-I	FAS-II
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	21	18	3
Units: number	68	2	2	0

End point values	Per Protocol Set (PPS)	PPS-I	PPS-II	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	17	3	
Units: number	2	2	0	

Statistical analyses

Statistical analysis title	overall study analysis
Comparison groups	run-in and main phase v Full Analysis Set (FAS) v FAS-I v FAS-II v Per Protocol Set (PPS) v PPS-I v PPS-II
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	multivariante analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

complete study

Assessment type	Systematic

Dictionary used

Dictionary name	CTC
Dictionary version	4.03

Reporting groups

Reporting group title	complete study

Reporting group description: -

Serious adverse events	complete study		
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 68 (69.12%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events	15		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
fever			

subjects affected / exposed	5 / 68 (7.35%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
General physical condition abnormal			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Multi-organ disorder			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Dyspnoea			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Psychiatric disorders			

Disorientation			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Creatinine urine increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ventricular failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac dysfunction			

subjects affected / exposed	4 / 68 (5.88%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Dementia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Cytopenia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroparesis postoperative			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Inguinal hernia				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 68 (4.41%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 68 (4.41%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Perforation				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Obstruction				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	4 / 68 (5.88%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstruction				

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	2 / 3		
Infection			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 2		
Pneumonia			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences causally related to treatment / all	6 / 12		
deaths causally related to treatment / all	0 / 3		
Cystitis			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anorexia nervosa			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	complete study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 68 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	10		
hypertensive crisis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
hypotension			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		

haematoma coccyx subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Hematoma Abdomen subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
hematoma subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 2		
deep vein thrombosis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
lymphedema face subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
phlebitis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	11 / 68 (16.18%) 27		
fever subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 18		
edema subjects affected / exposed occurrences (all)	7 / 68 (10.29%) 23		
weakness subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 8		
reduced general condition subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 4		
Pain			

subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	15		
Paravasat			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	7		
Mucositis			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	5		
Malaise			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Hematoma at port			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	8		
infusion site extravasation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
port infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
bleeding ulcus			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
tumefaction on injection site			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Immune system disorders			
allergic reaction			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		

Reproductive system and breast disorders			
pain in breast			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
BPH			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	20		
Cough			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	12		
sore throat			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Shortness of breath			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
throat pain			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
Bronchospasmus			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
rhinorrhea			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	13		

Confusion			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	4		
Restlessness			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	5		
Depression			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Anxiety			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
disorientation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
disorders of sleep			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
halluzination			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
aggression due to steroide			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
discomposure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Investigations			
creatinine increased			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Weight loss			

subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	9		
LDH increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
increase of hypertension			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
GGT increased			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Vitamin D shortage			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
PTT increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
AP increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
C-reactive protein increase			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Erythrocyte sedimentation rate increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
CRP increase			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	7		
Fracture			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
biceps tendon rupture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
pain (intermittent, after fall)			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Tachycardia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	5		
Atrial fibrillation			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	3		
Bradycardia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
pectangiose pain			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
cardiac decompensation			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
left ventricular systolic dysfunction			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
pericardial effusion			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
paroxysmal atrial flutter			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
palpitations			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
NYHA			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
heart pain			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
TAA			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
cardiac disorders			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	15		
Syncope			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Paresthesia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
trembling			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		

Loss of the smell subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Taste alteration subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2		
Headache subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
anomia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Tingling in the lower legs and feet subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
foot flexor paresis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
balance disorder subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
giddiness subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 7		
Leucopenia subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 42		
Anaemia			

subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	29		
Thrombocytopenia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	7		
Lymphocytopenia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Pancytopenia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Coagulation disorder			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	5		
Aural disturbances			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
hypakousis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
hearing impaired			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Eye disorders			
reduced visus			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
sight disorder			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
decreased vision			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
eye fibrillation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Gastrointestinal disorders			
Obstipation			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	42		
Vomiting			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	19		
Diarrhoea			
subjects affected / exposed	12 / 68 (17.65%)		
occurrences (all)	24		
Constipation			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	11		
Abdominal pain			
subjects affected / exposed	9 / 68 (13.24%)		
occurrences (all)	11		
Colitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
low-grade inflammation in mouth			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		

flatulence subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
heartburn subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
emesis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
oesophagitis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Fecal incontinence subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Dry mouth subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Hernia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 2		
Dysphagia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
incomplete intestinal obstruction subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Skin and subcutaneous tissue disorders sweat subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5		
suggilation subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
erythema			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
itching			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Exanthema due to medication			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Ulcus right lower leg			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
itching small-sized scaling Eczema left mamma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
alopecia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
rash intermittent			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
suspected Dermal eczema			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Renal and urinary disorders			
prerenal kidney failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
urinary tract obstruction			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Incontinence			

subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
acute renal failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	2		
nykturia			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
leukocyturia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
light burining while urination			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Renal Toxicity			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyreose			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
hyperthyreodism			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Pain subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 16		
Osteoporosis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
weakness subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 3		
muscle hypothrophy subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
swollen joint subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
gonarthrosis right subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Joint range of motion decreased - left shoulder subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	7 / 68 (10.29%) 15		
bronchitis subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 3		
Infection subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 13		
Herpes subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
soor			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Cold			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Mycosis			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Erysipelas			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Candida infection			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	10 / 68 (14.71%)		
occurrences (all)	30		
loss of appetite			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	12		
Anorexia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	9		
tumorlysis syndrom			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		

exsiccosis				
subjects affected / exposed	3 / 68 (4.41%)			
occurrences (all)	5			
Dehydration				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences (all)	2			
cancer cachexia - weight loss				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
Hyperglycaemia				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
tumor lysis syndrom				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
Hypocalcaemia				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences (all)	2			
hypovitaminosis				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
electrolyte imbalance				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
malnutrition				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
lack of protein				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	1			
Hypomagnesaemia				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences (all)	2			
Hyperuricaemia				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences (all)	2			

Hyponatraemia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2013	Changes for the main phase 2 of the trial (from patient 21) due to additional requested information by the Ethic committee during approval process
20 April 2015	- Reduction of planned number of patients (from 100 to 77 patients) to recruit for the study - Prolongation of recruitment time - Number of sites reduced
18 August 2017	Deletion of the interim analysis, due to premature termination of recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported