Clinical trial results:
Age-adjusted high-dose chemotherapy and autologous stem cell transplant in elderly and fit primary CNS lymphoma patients

Summary

EudraCT number	2016-001628-72
Trial protocol	DE
Global end of trial date	27 December 2021

Results information

Result version number	v1 (current)
This version publication date	24 November 2023
First version publication date	24 November 2023

Trial information

Trial identification

Sponsor protocol code	P001317

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00011932

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Hugstetter Straße 55, Freiburg, Germany, 79106
Public contact	PD Dr. med. Elisabeth Schorb, Universitätsklinikum Freiburg, Klinik für Innere Medizin I, 0049 761270-35361, elisabeth.schorb@uniklinik-freiburg.de
Scientific contact	PD Dr. med. Elisabeth Schorb, Universitätsklinikum Freiburg, Klinik für Innere Medizin I, 0049 761270-35361, elisabeth.schorb@uniklinik-freiburg.de

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	23 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2021
Global end of trial reached?	Yes
Global end of trial date	27 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to investigate the efficacy of age-adapted induction treatment followed by high-dose chemotherapy and autologous stem cell transplantation regarding 1-year PFS in elderly and fit patients with primary CNS lymphoma.

Protection of trial subjects:

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	28 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	0
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	54
Number of subjects completed	54

Period 1

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

Blinding implementation details:

Single arm trial, not blinded

Arms

Arm title	Induction treatment followed by high-dose chemo

Arm description:

Induction treatment: 2 cycles, stem-cell harvest after first cycle: rituximab 375 mg/m²/d i.v. (days 0, 4), MTX 3.5 g/m² i.v. (day 1), and Ara-C 2 x 2 g/m²/d i.v. (days 2-3) followed by Consolidation treatment: High-dose chemotherapy: rituximab 375 mg/m² i.v. (days -8), busulfan 3.2 mg/kg/d i.v. (days -7 and -6), thiotepa 5 mg/kg/d i.v. (days -5 and -4), ASCT (day 0)

Arm type	Experimental
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: 1875 mg/m2 (total), for induction and consolidation treatment

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/kg (total)

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	Concentrate for solution for infusion

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)

Dose: 10 mg/kg (total), for high-dose consolidation

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Methotrexat medac 100 mg/mL Injektionslösung
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Strength: 100 mg/mL MTX

Dose: 7 g/m2 (total), for induction treatment

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: 16 g/m2 (total), for induction treatment

Number of subjects in period 1	Induction treatment followed by high-dose chemo
Started	54
Completed	37
Not completed	17
Multiple reasons	17

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	54	54	
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)	0	0	
From 65-84 years	54	54	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	28	28	
Male	26	26	

Subject analysis sets	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS analysis is based on the data of 51 registered patients who received at least one administration of IMP and who had no major protocol deviations.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis was performed in the safety analysis set (SAF), comprising all patients for whom treatment was started. In case the SAF was restricted to those patients who received HD-ASCT, it was denoted as SAF-PP.

Reporting group values	Full analysis set (FAS)	Safety analysis set (SAF)	
Number of subjects	51	54	
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)	0	0	
From 65-84 years	51	54	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	27	28	
Male	24	26	

End points

End points reporting groups

Reporting group title	Induction treatment followed by high-dose chemo

Reporting group description:

Induction treatment: 2 cycles, stem-cell harvest after first cycle: rituximab 375 mg/m²/d i.v. (days 0, 4), MTX 3.5 g/m² i.v. (day 1), and Ara-C 2 x 2 g/m²/d i.v. (days 2-3) followed by Consolidation treatment: High-dose chemotherapy: rituximab 375 mg/m² i.v. (days -8), busulfan 3.2 mg/kg/d i.v. (days -7 and -6), thiotepa 5 mg/kg/d i.v. (days -5 and -4), ASCT (day 0)

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Primary: Progression-free survival

End point title	Progression-free survival[1]

End point description:

End point type	Primary

End point timeframe:

1 year from start of the induction treatment until disease progression or death, whichever occurred first.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single arm trial. The primary endpoint of the trial was PFS at 1 year, where PFS was defined as the time from start of treatment until disease progression or death, whichever occurred first. As no censored observations before 1 year occurred, the 1 year PFS rate was estimated based on the Binomial distribution, and exact CIs were derived.

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: % of patients				
number (confidence interval 80%)				
PFS at 1 year	58.8 (48.9 to 68.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission after induction treatment

End point title	Complete Remission after induction treatment

End point description:

End point type	Secondary

End point timeframe:
after induction treatment

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Number of patients				
Complete remission	3			
Unconfirmed complete remission	3			
Partial Remission	36			
Stable disease	2			
Progressive disease	1			
Missing evaluation and death before day 43	5			
Missing evaluation	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:
from start of induction treatment

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: % of patients				
number (confidence interval 80%)				
3 months	86.3 (78.7 to 91.3)			
6 months	68.6 (59.5 to 76.1)			
12 months	58.8 (49.5 to 67.0)			

18 months	55.9 (46.2 to 64.5)			
24 months	55.9 (46.2 to 64.5)			
36 months	55.9 (46.2 to 64.5)			
48 months	37.3 (17.9 to 56.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission on day 30 after HDT-ASCT

End point title	Complete Remission on day 30 after HDT-ASCT

End point description:

End point type	Secondary

End point timeframe:

30 after HDT-ASCT

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Number of patients				
Complete Remission	11			
Unconfirmed complete remission	12			
Partial remission	12			
Missing eval. and death/progr. before day 120	12			
Mission evaluation	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

from start of induction treatment

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: % of patients				
number (confidence interval 95%)				
3 months	88.2 (75.7 to 94.5)			
6 months	72.5 (58.1 to 82.7)			
12 months	62.7 (48.0 to 74.4)			
18 months	60.1 (45.1 to 72.2)			
24 months	60.1 (45.1 to 72.2)			
36 months	60.1 (45.1 to 72.2)			
48 months	34.4 (8.7 to 62.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Non Relapse Mortality

End point title	Non Relapse Mortality

End point description:

End point type	Secondary

End point timeframe:

from start of induction treatment

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Cumulative incidence				
number (confidence interval 95%)				
3 months	0.1176 (0.0473 to 0.2230)			
6 months	0.2353 (0.1294 to 0.3592)			

12 months	0.2745 (0.1599 to 0.4019)			
18 months	0.2745 (0.1599 to 0.4019)			
24 months	0.2745 (0.1599 to 0.4019)			
36 months	0.2745 (0.1599 to 0.4019)			
48 months	0.4608 (0.1070 to 0.7644)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse rate

End point title	Relapse rate

End point description:

End point type	Secondary

End point timeframe:

from start of induction treatment

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Cumulative incidence				
number (confidence interval 95%)				
3 months	0.0196 (0.0015 to 0.0919)			
6 months	0.0784 (0.0247 to 0.1737)			
12 months	0.1373 (0.0595 to 0.2472)			
18 months	0.1667 (0.0756 to 0.2885)			
24 months	0.1667 (0.0756 to 0.2885)			
36 months	0.1667 (0.0756 to 0.2885)			

48 months	0.1667 (0.0756 to 0.2885)			

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-30 - Global health status

End point title	EORTC QLQ-30 - Global health status

End point description:

End point type	Secondary

End point timeframe:

During trial

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Points (QLQ-30)				
arithmetic mean (standard deviation)				
Screening	51.5 (± 26.4)			
Response assessment I	58.1 (± 21.0)			
Response assessment II (EOT)	56.5 (± 24.9)			
Change from screening to EOT	-0.4 (± 25.7)			
1 year follow-up	70.2 (± 22.9)			
1 year FU: change from screening	14.8 (± 30.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Activities of Daily Life

End point title	Activities of Daily Life

End point description:

End point type	Secondary

End point timeframe:

during trial

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Points (ADL)				
arithmetic mean (standard deviation)				
Screening	14.9 (± 6.0)			
Response assessment I	15.0 (± 5.7)			
Response assessment II (EOT)	15.6 (± 5.9)			
Change from screening to EOT	-0.7 (± 4.6)			
1 year follow-up	17.2 (± 5.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mini-Mental Status Examination

End point title	Mini-Mental Status Examination

End point description:

End point type	Secondary

End point timeframe:
during trial

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Points				
arithmetic mean (standard deviation)				
Screening	23.4 (± 6.4)			
Response assessment I	24.9 (± 5.2)			
Response assessment II (EOT)	25.6 (± 5.8)			
Change from screening to EOT	2.5 (± 3.9)			
1 year follow-up	26.3 (± 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neuro-psychological assessment

End point title	Neuro-psychological assessment

End point description:

End point type	Secondary
End point timeframe:	
Day 30 after EOT/ASCT	

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Points / sec				
median (full range (min-max))				
Digit span forward [points]	9.5 (6 to 16)			
Digit span backward [points]	5 (2 to 11)			
Digit span total [points]	15 (9 to 24)			
Short-term recall total [points]	16.5 (3 to 28)			
Short-term recall delayed [points]	5 (0 to 12)			
Brief test of attention: digits [points]	7 (1 to 10)			
Brief test of attention: letters [points]	6 (0 to 10)			
Brief test of attention total [points]	13 (1 to 19)			
Trail making test A [sec]	57 (24 to 180)			
Trail making test B [sec]	122 (66 to 300)			
Grooved pegboard right [sec]	104 (0 to 280)			
Grooved Pegboard left [sec]	104 (64 to 517)			
Total of correct positive answers [points]	12 (0 to 12)			
Semantically related false positive answers [point	0 (0 to 6)			
Semantically not related false positive answers [p	0 (0 to 6)			

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	Induction treatment followed by high-dose chemo

Reporting group description:

Induction treatment: Rituximab 375 mg/m²/d i.v. (d0,4)+MTX 3,5 g/m² i.v. (d1)+AraC 2x2 g/m²/d i.v. (d2-3) Consolidation: Rituximab 375 mg/m² i.v. (d-8)+Busulfan 3,2 mg/kg/d i.v. (d-7 and d-6)+Thiotepa 5 mg/kg/d i.v. (d-5 and d-4)+ASCT (d0)

Serious adverse events	Induction treatment followed by high-dose chemo		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 54 (51.85%)		
number of deaths (all causes)	22		
number of deaths resulting from adverse events	10		
General disorders and administration site conditions			
Injection site necrosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dysarthria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Neurotoxicity			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Haematotoxicity			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Thrombocytopenia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic colitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Stevens-Johnson syndrome				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	4 / 54 (7.41%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical spinal stenosis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				

subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neutropenic infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 54 (11.11%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	1 / 2			
Urinary tract infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
Septic shock				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypokalaemia				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Induction treatment followed by high-dose chemo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)		
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Haematoma			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	26 / 54 (48.15%)		
occurrences (all)	29		
Hypotension			
subjects affected / exposed	20 / 54 (37.04%)		
occurrences (all)	23		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	26 / 54 (48.15%)		
occurrences (all)	33		
Gait disturbance			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Generalised oedema			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	23 / 54 (42.59%)		
occurrences (all)	28		
Pain			
subjects affected / exposed	16 / 54 (29.63%)		
occurrences (all)	17		
Pyrexia			
subjects affected / exposed	18 / 54 (33.33%)		
occurrences (all)	21		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Vulvovaginal erythema			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
Dysphonia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	11 / 54 (20.37%)		
occurrences (all)	12		
Epistaxis			

subjects affected / exposed	12 / 54 (22.22%)		
occurrences (all)	12		
Hypoxia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Confusional state			
subjects affected / exposed	22 / 54 (40.74%)		
occurrences (all)	28		
Delirium			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	7		
Disorientation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Hallucination			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	11		
Restlessness			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	51 / 54 (94.44%)		
occurrences (all)	77		
Aspartate aminotransferase increased			
subjects affected / exposed	30 / 54 (55.56%)		
occurrences (all)	44		
Blood creatinine increased			
subjects affected / exposed	22 / 54 (40.74%)		
occurrences (all)	28		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	17 / 54 (31.48%)		
occurrences (all)	20		
Blood fibrinogen decreased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
C-reactive protein increased			

subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Blood lactate dehydrogenase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Forced expiratory volume decreased			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	43 / 54 (79.63%)		
occurrences (all)	61		
Lymphocyte count decreased			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pancreatic enzymes increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	43 / 54 (79.63%)		
occurrences (all)	63		
White blood cell count decreased			
subjects affected / exposed	52 / 54 (96.30%)		
occurrences (all)	89		
Weight increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	8		
Fracture			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infusion related reaction			

subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Thermal burn			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Arrhythmia			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Atrial fibrillation			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	6		
Atrioventricular block first degree			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Diastolic dysfunction			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	8		
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	10		
Dysarthria			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dysdiadochokinesis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Facial paresis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	11 / 54 (20.37%)			
occurrences (all)	14			
Hemiparesis				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	4			
Hypoaesthesia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Leukoencephalopathy				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Memory impairment				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Monoparesis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Paraesthesia				
subjects affected / exposed	8 / 54 (14.81%)			
occurrences (all)	8			
Peripheral motor neuropathy				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Presyncope				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	8 / 54 (14.81%)		
occurrences (all)	9		
Syncope			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Transient ischaemic attack			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Seizure			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	54 / 54 (100.00%)		
occurrences (all)	91		
Febrile neutropenia			
subjects affected / exposed	32 / 54 (59.26%)		
occurrences (all)	41		
Leukocytosis			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	54 / 54 (100.00%)		
occurrences (all)	91		
Thrombocytopenic purpura			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ulcerative keratitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 54 (24.07%)		
occurrences (all)	14		
Anal erythema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Diverticulum intestinal			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	21 / 54 (38.89%)		
occurrences (all)	23		
Diarrhoea			

subjects affected / exposed	22 / 54 (40.74%)			
occurrences (all)	25			
Diverticulum				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Gastrointestinal inflammation				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Dysphagia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Gastrooesophageal reflux disease				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Neutropenic colitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Mouth haemorrhage				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	25 / 54 (46.30%)			
occurrences (all)	32			
Oesophagitis				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pancreatitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	36 / 54 (66.67%)		
occurrences (all)	39		
Vomiting			
subjects affected / exposed	16 / 54 (29.63%)		
occurrences (all)	17		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hepatic cyst			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hepatic pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hepatic steatosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Drug eruption			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Intertrigo			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Skin fissures			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Chronic kidney disease			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Haematuria			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Incontinence			

subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Polyuria subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Renal cyst subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Urinary tract obstruction subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4		
Urinary retention subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Urinary tract pain subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Back pain subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Bone pain			

subjects affected / exposed	11 / 54 (20.37%)		
occurrences (all)	12		
Muscle spasms			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Anorectal infection bacterial			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Bacteraemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Bacterial tracheitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Clostridium difficile infection			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Device related infection			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	6		
Escherichia infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Eye infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Febrile infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Injection site abscess				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Laryngitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Mucosal infection				
subjects affected / exposed	9 / 54 (16.67%)			
occurrences (all)	11			
Neutropenic sepsis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	4			
Rash pustular				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Respiratory moniliasis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			

Sepsis subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 4		
Septic encephalopathy subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Septic shock subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Skin infection subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Soft tissue infection subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Staphylococcal infection subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 54 (12.96%) 8		
Vascular device infection subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 5		
Dehydration subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Hyperglycaemia			

subjects affected / exposed	18 / 54 (33.33%)			
occurrences (all)	27			
Hyperkalaemia				
subjects affected / exposed	9 / 54 (16.67%)			
occurrences (all)	9			
Hypernatraemia				
subjects affected / exposed	7 / 54 (12.96%)			
occurrences (all)	10			
Hyperphosphataemia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Hypertriglyceridaemia				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Hyperuricaemia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Hypoalbuminaemia				
subjects affected / exposed	4 / 54 (7.41%)			
occurrences (all)	4			
Hypocalcaemia				
subjects affected / exposed	4 / 54 (7.41%)			
occurrences (all)	4			
Hypokalaemia				
subjects affected / exposed	27 / 54 (50.00%)			
occurrences (all)	37			
Hypomagnesaemia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Hyponatraemia				
subjects affected / exposed	17 / 54 (31.48%)			
occurrences (all)	22			
Hypophosphataemia				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Steroid diabetes				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Tumour lysis syndrome			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/30925912