Clinical trial results:
Thiotepa- Fludarabine- Treosulfan (TFT) conditioning for 2nd allogeneic PBSCT from a different unrelated donor in patients with AML relapsing from prior allogeneic HCT

Konditionierung mit Thiotepa-Fludarabin-Treosulfan (TFT) bei zweiter allogener Stammzelltranplantation von einem anderen nicht verwandten Spender für Patienten mit Rezidiv einer AML nach 1. allogener Stammzelltransplantation

Summary

EudraCT number	2012-005414-18
Trial protocol	DE
Global end of trial date	17 April 2020

Results information

Result version number	v1 (current)
This version publication date	14 May 2022
First version publication date	14 May 2022

Trial information

Trial identification

Sponsor protocol code	ZKS000783

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00005126

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Dr. med. Olga Grichina, Clinical Trials Unit, Medical Center - University of Freiburg, +49 761270-74410, olga.grichina@uniklinik-freiburg.de
Scientific contact	Prof. Dr. med. Jürgen Finke, Department of Medicine I, Medical Center - University of Freiburg, +49 761270-33640, juergen.finke@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	13 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 April 2020
Global end of trial reached?	Yes
Global end of trial date	17 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the probability of disease-free survival (DFS), defined as being alive and free of relapse at 1 year after 2nd allogeneic Peripheral Blood Stem Cell Transplantation (PBSCT, 2nd Tx) from unrelated donors after a uniform "intensive-RIC" conditioning with the TFT regimen and defined Graft-versus-Host-Disease (GvHD) prophylaxis

Protection of trial subjects:

The clinical trial was designed in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The protocol and the proposed informed consent form was reviewed and approved by a properly constituted Independent Ethics Committee (IEC of the University of Freiburg) before trial start.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

52 patients were registered for the study from 25th March 2014 up to 10th March 2017 from 9 German centres

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	52
Number of subjects completed	52

Period 1

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

Arms

Arm title	2nd alloHC after conditioning regimen and GvHD propyhlaxis

Arm description:

2nd allogenic peripheral blood hematopoietic cell transplantation (HCT) from an unrelated donor after a uniform conditioning with Treosulfan 3x12g/m2, Fludarabin 3x30mg/m2, and Thiotepa 3x 5mg/kg (TFT), and Graft versus Host Disease (GvHD) prophylaxis with cyclosporine A (CyA) /Mycophenolate and ATG-F (Neovii) 3x10mg/kg.

Arm type	Experimental
Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3x 5 mg/kg

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

Dosage and administration details:

3x12 g/m2

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

3x30 mg/m2

Number of subjects in period 1	2nd alloHC after conditioning regimen and GvHD propyhlaxis
Started	52
Completed	52

Baseline characteristics

Reporting groups

Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	52	52	
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)	50	50	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	48.9		
standard deviation	± 12.5	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	33	33	

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all patients registered for the study, for whom the conditioning regimen TFT and the GvHD prophylaxis regimen Cyclosporine A (CyA), Mycophenolic Acid (MPA) / Mycophenolate mofetil (MMF), ATG-F has started, and for whom allogeneic PBSCT from an unrelated donor has been performed.

Reporting group values	FAS		
Number of subjects	50		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	48		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	49.6		
standard deviation	± 12.1		
Gender categorical			
Units: Subjects			
Female	18		
Male	32		

End points

End points reporting groups

Reporting group title	2nd alloHC after conditioning regimen and GvHD propyhlaxis

Reporting group description:

2nd allogenic peripheral blood hematopoietic cell transplantation (HCT) from an unrelated donor after a uniform conditioning with Treosulfan 3x12g/m2, Fludarabin 3x30mg/m2, and Thiotepa 3x 5mg/kg (TFT), and Graft versus Host Disease (GvHD) prophylaxis with cyclosporine A (CyA) /Mycophenolate and ATG-F (Neovii) 3x10mg/kg.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all patients registered for the study, for whom the conditioning regimen TFT and the GvHD prophylaxis regimen Cyclosporine A (CyA), Mycophenolic Acid (MPA) / Mycophenolate mofetil (MMF), ATG-F has started, and for whom allogeneic PBSCT from an unrelated donor has been performed.

Primary: Disease-free survival (DFS)

End point title	Disease-free survival (DFS)[1]

End point description:

Defined as being alive and free of relapse at 12 months post 2nd Tx.

End point type	Primary

End point timeframe:

12 months post 2nd Tx

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 phase II trial, comparison with historical control data.

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probabilty of DFS				
number (confidence interval 95%)	0.46 (0.318 to 0.607)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse

End point title	Relapse

End point description:

Probability of relapse at 36 months after 2nd TX

End point type	Secondary

End point timeframe:

36 months after 2nd TX

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability of relapse				
number (confidence interval 95%)	0.36 (0.25 to 0.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse mortality

End point title	Relapse mortality
End point description: Probability of relapse mortality at 36 months after 2nd TX	
End point type	Secondary
End point timeframe: 36 months after 2nd TX	

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.35 (0.24 to 0.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-relapse mortality

End point title	Non-relapse mortality
End point description: Probability of non-relapse mortality at 36 months after 2nd TX	
End point type	Secondary
End point timeframe: 36 months after 2nd TX	

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probabilty				
number (confidence interval 95%)	0.40 (0.29 to 0.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
End point description:	
Probability of overall survival at 36 months after 2nd TX	
End point type	Secondary
End point timeframe:	
36 months after 2nd TX	

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.24 (0.13 to 0.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute graft versus host disease (aGvHD) any

End point title	Acute graft versus host disease (aGvHD) any
End point description:	
End point type	Secondary
End point timeframe:	
6 months	

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.54 (0.42 to 0.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute graft versus host disease (aGvHD) Grade II-IV

End point title	Acute graft versus host disease (aGvHD) Grade II-IV

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.42 (0.30 to 0.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute graft versus host disease (aGvHD) Grade III-IV

End point title	Acute graft versus host disease (aGvHD) Grade III-IV

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.26 (0.16 to 0.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic graft versus host disease (cGvHD) any

End point title	Chronic graft versus host disease (cGvHD) any

End point description:

End point type	Secondary

End point timeframe:

12 months post 2nd TX

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.26 (0.16 to 0.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic graft versus host disease (cGvHD) extensive (Seattle)

End point title	Chronic graft versus host disease (cGvHD) extensive (Seattle)

End point description:

Probability of extensive (Seattle) chronic GvHD at 12 months post 2nd TX

End point type	Secondary

End point timeframe:

12 months post 2nd TX

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.20 (0.12 to 0.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic graft versus host disease (cGvHD) moderate/severe (NIH)

End point title	Chronic graft versus host disease (cGvHD) moderate/severe (NIH)

End point description:

End point type	Secondary

End point timeframe:

12 months post 2nd TX

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.22 (0.13 to 0.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: ECOG performance status

End point title	ECOG performance status

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Number of patients				
Grade 0	7			
Grade 1	16			
Grade 2	1			
Grade 3	0			
Grade 4	0			
Grade 5	0			
Missing	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Engraftment (ANC>0.5/nL)

End point title	Engraftment (ANC>0.5/nL)

End point description:

End point type	Secondary

End point timeframe:

at 3 months and at 6 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.94 (0.87 to 1.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Engraftment (ANC>1.0/nL)

End point title	Engraftment (ANC>1.0/nL)

End point description:

End point type	Secondary

End point timeframe:
at 3 months and at 6 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.92 (0.85 to 1.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet engraftment (platelets>20/nL)

End point title	Platelet engraftment (platelets>20/nL)

End point description:
Probability of engraftment (platelets >20/nL)

End point type	Secondary

End point timeframe:
at 3 months and 6 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.80 (0.70 to 0.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet engraftment (platelets>100/nL)

End point title	Platelet engraftment (platelets>100/nL)

End point description:
Probability of engraftment (platelets >100/nL)

End point type	Secondary

End point timeframe:
at 3 months and at 6 months

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Probability				
number (confidence interval 95%)	0.62 (0.50 to 0.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival (DSF)

End point title	Disease-free survival (DSF)

End point description:

Median DFS time post 2nd Tx, defined as time from 2nd Tx until relapse or death.

End point type	Secondary

End point timeframe:

Time from 2nd Tx until relapse or death

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: DSF time				
median (confidence interval 95%)	8.69 (2.76 to 32.16)			

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	23

Reporting groups	
Reporting group title	Overall
Reporting group description:	
2nd alloHC after conditioning regimen and GvHD propyhlaxis	

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 52 (55.77%)		
number of deaths (all causes)	39		
number of deaths resulting from adverse events	15		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Stomatitis			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral toxoplasmosis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cytomegalovirus infection reactivation			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Febrile infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster disseminated				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Herpes zoster				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster meningoencephalitis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metapneumovirus infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				

subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oesophageal infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 52 (11.54%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	1 / 4			
Pulmonary sepsis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	7 / 52 (13.46%)			
occurrences causally related to treatment / all	4 / 7			
deaths causally related to treatment / all	2 / 5			
Septic shock				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	1 / 2			
Upper respiratory tract infection				

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral haemorrhagic cystitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 52 (100.00%)		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	15 / 52 (28.85%)		
occurrences (all)	15		
Hypotension			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Jugular vein thrombosis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Venoocclusive disease			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Extravasation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Localised oedema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Mucosal haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	32 / 52 (61.54%)		
occurrences (all)	32		
Oedema peripheral			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	9		
Oedema			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Pain			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	17 / 52 (32.69%)		
occurrences (all)	20		
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Hypoxia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Interstitial lung disease			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Obstructive airways disorder			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pharyngeal inflammation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Respiratory failure			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hallucination			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Intentional self-injury			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Organic brain syndrome			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Product issues			
Liquid product physical issue			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Aspartate aminotransferase increased				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Biopsy soft tissue				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood albumin decreased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood bilirubin increased				
subjects affected / exposed	14 / 52 (26.92%)			
occurrences (all)	24			
Blood calcium decreased				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Blood cholinesterase decreased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	10 / 52 (19.23%)			
occurrences (all)	16			
Blood culture positive				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood immunoglobulin G decreased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood lactate dehydrogenase increased				

subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood thyroid stimulating hormone increased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Blood magnesium decreased				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Blood urea increased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
C-reactive protein increased				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Gamma-glutamyltransferase increased				
subjects affected / exposed	7 / 52 (13.46%)			
occurrences (all)	8			
Haemoglobin decreased				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	4			
Liver function test increased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Oxygen saturation decreased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Platelet count decreased				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Thyroxine free decreased				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Troponin T increased				

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tri-iodothyronine free decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Transfusion-related acute lung injury			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Cardiac failure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pericardial effusion			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Sinus tachycardia			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Tachycardia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Cerebral ischaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Encephalopathy			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Myoclonus			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	11		
Coagulopathy			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Febrile neutropenia			
subjects affected / exposed	12 / 52 (23.08%)		
occurrences (all)	12		
Haemolysis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Pancytopenia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	11 / 52 (21.15%)		
occurrences (all)	12		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Lacrimation increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pupils unequal			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	29 / 52 (55.77%)		
occurrences (all)	32		
Duodenitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Dysphagia				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Haematemesis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Ileus				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Large intestinal stenosis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Lip disorder				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Mouth haemorrhage				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Nausea				
subjects affected / exposed	37 / 52 (71.15%)			
occurrences (all)	43			
Neutropenic colitis				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			

Oral blood blister			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Oesophagitis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	3		
Proctalgia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Subileus			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	19 / 52 (36.54%)		
occurrences (all)	21		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hydrocholecystis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Liver disorder			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Alopecia			

subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Decubitus ulcer				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Dermatitis exfoliative generalised				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Drug eruption				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	4			
Petechiae				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Rash				
subjects affected / exposed	16 / 52 (30.77%)			
occurrences (all)	17			
Rash maculo-papular				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Skin fissures				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			

Skin hyperpigmentation subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Skin lesion subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Skin ulcer subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 5		
Bladder spasm subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Dysuria subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Haematuria subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Pollakiuria subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Muscle spasms subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 2		
Myalgia			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Anal abscess			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
BK virus infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Atypical pneumonia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Bacterial infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Bacterial sepsis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Candida infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Clostridium difficile colitis			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Coronavirus infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Cystitis bacterial				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Cytomegalovirus colitis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Cytomegalovirus infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Cytomegalovirus infection reactivation				
subjects affected / exposed	8 / 52 (15.38%)			
occurrences (all)	8			
Device related infection				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	4			
Enterococcal sepsis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Enterobacter infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Epstein-Barr virus infection reactivation				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Eye infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Escherichia sepsis				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Fusarium infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Gastroenteritis adenovirus				

subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Gastrointestinal candidiasis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Herpes simplex reactivation				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Herpes simplex				
subjects affected / exposed	5 / 52 (9.62%)			
occurrences (all)	5			
Herpes zoster				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Human herpesvirus 6 infection reactivation				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	4			
Klebsiella infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Oral candidiasis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Pneumonia				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Pulmonary mycosis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			

Pseudomonal sepsis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Relapsing fever				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Sepsis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Soft tissue infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Staphylococcal infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Staphylococcal sepsis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Urinary tract infection enterococcal				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			

Urinary tract infection subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 9		
Vascular device infection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Hyperglycaemia subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 5		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Hypernatraemia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Hypocalcaemia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 52 (21.15%) 13		
Hyponatraemia			

subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	5		
Hypophosphataemia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypoproteinaemia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		

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