Clinical trial results:
Prospective, open-label, randomised, two-arm, controlled, multicentre clinical trial, phase I/IIa, for the evaluation of safety and efficacy of an adoptive immunotherapy with allogeneic CMV-/EBV-specific peptide-stimulated T-cells (CD3+) for the prevention or treatment of reactivation of 'CMV and/or EBV in patients after allogeneic HLA-identical stem cell transplantation

Summary

EudraCT number	2012-004240-30
Trial protocol	DE
Global end of trial date	26 April 2019

Results information

Result version number	v1 (current)
This version publication date	03 July 2020
First version publication date	03 July 2020

Trial information

Trial identification

Sponsor protocol code	AIT-MULTIVIR-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Erlangen
Sponsor organisation address	Maximiliansplatz 2, Erlangen, Germany, 91054
Public contact	Direktion Medizinische Klinik 5, Medizinische Klinik 5, Universitätsklinikum Erlangen, +49 09131 85 35954, andreas.mackensen@uk-erlangen.de
Scientific contact	Direktion Medizinische Klinik 5, Medizinische Klinik 5, Universitätsklinikum Erlangen, +49 09131 85 35954, andreas.mackensen@uk-erlangen.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	26 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2019
Global end of trial reached?	Yes
Global end of trial date	26 April 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the safety and tolerability of an adoptive immunotherapy with CMV-/EBV-specific peptide-stimulated T-cells (CD3+) for prevention or treatment of the reactivation of CMV or EBV infection in patients after allogeneic HLA-identical stem cell transplantation.

Protection of trial subjects:

IMP sterility and purity testing, Premedication with antihistaminics, cardiopulmonal Monitoring

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	23
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening and randomization -> SCT -> Eligibility check Prior to IMP Administration -> final enrollment -> IMP admin. (Verum)/watch and wait (Control)

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum1

Arm description:

Subjects randomized to IMP

Arm type	Experimental
Investigational medicinal product name	Allogeneic CMV-/EBV-specific peptide-stimulated T-cells (CD3+)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

20.000 - 50.000 cells per kg BW, 3 applications (day 1/30/60 = day 30/60/90 after stem cell Transplantation)

Arm title	Control1

Arm description:

Subjects randomized to Control

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Verum1	Control1
Started	16	13
Completed	16	13

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

Arms	
Are arms mutually exclusive?	Yes
Arm title	Verum2

Arm description:

Subjects randomized to IMP who passed eligibility Evaluation (V2) and for whom IMP could be produced

Arm type	Experimental
Investigational medicinal product name	Allogeneic CMV-/EBV-specific peptide-stimulated T-cells (CD3+)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

20.000 - 50.000 cells per kg BW, 3 applications (day 1/30/60 = day 30/60/90 after stem cell Transplantation)

Arm title	Control2

Arm description:

Subjects randomized to Control plus subjects randomized to Verum but IMP could not be produced

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Verum2	Control2
Started	16	13
Completed	9	16
Not completed	7	0
Consent withdrawn by subject	2	-
Physician decision	2	-
Transferred to other arm/group	3	-
Joined	0	3
Transferred in from other group/arm	-	3

Period 3	
Period 3 title	Treatment and Follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Verum3

Arm description:

Subjects with at least one IMP administered

Arm type	Experimental
Investigational medicinal product name	Allogeneic CMV-/EBV-specific peptide-stimulated T-cells (CD3+)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

20.000 - 50.000 cells per kg BW, 3 applications (day 1/30/60 = day 30/60/90 after stem cell Transplantation)

Arm title	Control3

Arm description:

Subjects from Control2 who reached EoS (day 204)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Verum3	Control3
Started	9	16
Completed	9	14
Not completed	0	2
Adverse event, non-fatal	-	1
Relaps underlying disease (AML)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Verum1
Reporting group description:	
Subjects randomized to IMP	
Reporting group title	Control1
Reporting group description:	
Subjects randomized to Control	

Reporting group values	Verum1	Control1	Total
Number of subjects	16	13	29
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	57.2	56.3	
full range (min-max)	29 to 75	25 to 74	-
Gender categorical			
Units: Subjects			
Female	3	1	4
Male	13	12	25

End points

End points reporting groups

Reporting group title	Verum1
Reporting group description: Subjects randomized to IMP	
Reporting group title	Control1
Reporting group description: Subjects randomized to Control	
Reporting group title	Verum2
Reporting group description: Subjects randomized to IMP who passed eligibility Evaluation (V2) and for whom IMP could be produced	
Reporting group title	Control2
Reporting group description: Subjects randomized to Control plus subjects randomized to Verum but IMP could not be produced	
Reporting group title	Verum3
Reporting group description: Subjects with at least one IMP administered	
Reporting group title	Control3
Reporting group description: Subjects from Control2 who reached EoS (day 204)	

Primary: Occurrence of acute toxicity

End point title	Occurrence of acute toxicity[1]
End point description: e.g. allergic or anaphylactic reaction CTCAE>= 2	
End point type	Primary
End point timeframe: within 72 Hours after Administration of the IMP	

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: Toxicity could occur only in Verum Group (Control: no IMP given); as no toxicity was reported, no statistical Analysis necessary

End point values	Verum3			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: events	0			

Statistical analyses

No statistical analyses for this end point

Primary: De novo onset of acute GvHD within 14 days after administration of the IMP

End point title	De novo onset of acute GvHD within 14 days after administration of the IMP[2]

End point description:

End point type	Primary

End point timeframe:

at all visits during Treatment and follow up period

Notes:

[2] - 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: Acute GvHD within 14 days after IMP administration could occur only in Verum Group (Control: no IMP given); as no Acute GvHD within 14 days after IMP administration was reported, no statistical Analysis necessary

End point values	Verum3			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: events	0			

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of an aggravation of pre-existing acute GvHD (persistent acute GvHD) within 14 days after administratin of the IMP

End point title	Occurrence of an aggravation of pre-existing acute GvHD (persistent acute GvHD) within 14 days after administratin of the IMP[3]

End point description:

End point type	Primary

End point timeframe:

at all visits during Treatment and follow-up period

Notes:

[3] - 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: Endpoint could occur only in Verum Group (Control: no IMP given); as no Aggravation of a pre-existing acute GvHD was reported, no statistical Analysis necessary

End point values	Verum3			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: events	0			

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of at least one CMV reactivation

End point title	Occurrence of at least one CMV reactivation

End point description:

End point type	Primary

End point timeframe:

at all visits during the Treatment and follow-up period

End point values	Verum3	Control3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: event	4	9		

Attachments (see zip file)	Cum incid CMV reactivation/Graph_CMV_reactivation.png

Statistical analyses

Statistical analysis title	CMV reactivation Chi squared
Comparison groups	Verum3 v Control3
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.349
Method	Chi-squared

Statistical analysis title	CMV reactivation log-rank test
Comparison groups	Verum3 v Control3
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Logrank

Secondary: Occurrence of at least one EBV reactivation

End point title	Occurrence of at least one EBV reactivation

End point description:

End point type	Secondary

End point timeframe:

at all visits during the Treatment and follow-up period

End point values	Verum3	Control3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: event	7	6		

Statistical analyses

Statistical analysis title	EBV reactivation
Comparison groups	Verum3 v Control3
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099
Method	Chi-squared

Secondary: Occurrence of CMV viral load requiring treatment, cumulative dose valganciclovir

End point title	Occurrence of CMV viral load requiring treatment, cumulative dose valganciclovir

End point description:

End point type	Secondary

End point timeframe:

at all visits during the Treatment and follow-up period

End point values	Verum3	Control3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6[4]		
Units: mg				
arithmetic mean (standard deviation)	26550 (± 20238)	32721 (± 18680)		

Notes:

[4] - Control Group: 14 subjects; cmv reactivation: 9 subjects; Treatment with valganciclovir: 6 subjects

Statistical analyses

Statistical analysis title	T-test
Comparison groups	Verum3 v Control3

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621
Method	t-test, 2-sided

Secondary: Occurrence of EBV viral load requiring treatment

End point title	Occurrence of EBV viral load requiring treatment

End point description:

End point type	Secondary

End point timeframe:

at all visits during the Treatment and follow-up period

End point values	Verum3	Control3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[5]	6[6]		
Units: subjects	3	3		

Notes:

[5] - Verum Group: 9 subjects, EBV reactivation: 7 subjects, Treatment with Rituximab: 3 subjects

[6] - Control Group: 14 subjects, EBV reactivation: 6 subjects, Treatment with Rituximab: 3 subjects

Statistical analyses

Statistical analysis title	Chi squared
Comparison groups	Verum3 v Control3
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.343
Method	Chi-squared

Secondary: De novo onset of acute GvHD

End point title	De novo onset of acute GvHD

End point description:

End point type	Secondary

End point timeframe:

at all visits during Treatment and follow up period

End point values	Verum3	Control3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: event	3	7		

Attachments (see zip file)	Logrank_cumulative_incidence_acute_GvHD.pdf

Statistical analyses

Statistical analysis title	Logrank
Comparison groups	Verum3 v Control3
Number of subjects included in analysis	23
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.55
Method	Logrank

Secondary: Occurrence of CMV viral load requiring treatment, days of valganciclovir treatment

End point title	Occurrence of CMV viral load requiring treatment, days of valganciclovir treatment

End point description:

End point type	Secondary

End point timeframe:

at all visits during the Treatment and follow-up period

End point values	Verum3	Control3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: days				
arithmetic mean (standard deviation)	22.00 (± 17.5)	37.14 (± 28.4)		

Statistical analyses

Statistical analysis title	t-test
Comparison groups	Verum3 v Control3

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.365
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
from day 1 (day of first IMP Administration, for Control Group day 1 = day 28 after SCT) until day 204 after SCT	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Verum (IMP administered)
Reporting group description:	
patients who switched from Verum to Control Group without any IMP administered were assigned to the reporting group "Control (no IMP administered)"	
Reporting group title	Control (no IMP administered)
Reporting group description:	
Patients who were randomized to the Verum Group but switched to the Control Group without any IMP Administration were assigned to the reporting Group "Control (no IMP administered)"	

Serious adverse events	Verum (IMP administered)	Control (no IMP administered)	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	10 / 16 (62.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Joint arthroplasty			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Radiculopathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in liver			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 9 (0.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	3 / 9 (33.33%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Verum (IMP administered)	Control (no IMP administered)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	16 / 16 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chloroma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Plasma cell myeloma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	3	
Haematoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
hypertension			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	1	3	
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Circulatory collapse			

subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	4 / 9 (44.44%)	1 / 16 (6.25%)	
occurrences (all)	8	1	
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	6 / 16 (37.50%)	
occurrences (all)	0	7	
Oedema peripheral			
subjects affected / exposed	2 / 9 (22.22%)	1 / 16 (6.25%)	
occurrences (all)	5	2	
Chills			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Immune system disorders			

Acute graft versus host disease			
subjects affected / exposed	1 / 9 (11.11%)	3 / 16 (18.75%)	
occurrences (all)	4	4	
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 9 (11.11%)	5 / 16 (31.25%)	
occurrences (all)	2	6	
Acute graft versus host disease in intestine			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Chronic graft versus host disease			
subjects affected / exposed	2 / 9 (22.22%)	3 / 16 (18.75%)	
occurrences (all)	3	4	
Chronic graft versus host disease in skin			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Chronic graft versus host disease in intestine			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Graft versus host disease in liver			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Graft versus host disease			
subjects affected / exposed	2 / 9 (22.22%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Secondary immunodeficiency			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea exertional			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oral mucosal blistering			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Confusional state			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	10	
Hypoalbuminaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 9 (22.22%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Alpha hydroxybutyrate dehydrogenase increased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	2		
Amylase increased				
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 9 (0.00%)	3 / 16 (18.75%)		
occurrences (all)	0	10		
Blood pressure increased				
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Clostridium test positive				
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
C-reactive protein increased				
subjects affected / exposed	2 / 9 (22.22%)	0 / 16 (0.00%)		
occurrences (all)	2	0		
Electrolyte depletion				
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Electrophoresis abnormal				
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Serum ferritin increased				
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Blood folate decreased				
subjects affected / exposed	0 / 9 (0.00%)	3 / 16 (18.75%)		
occurrences (all)	0	3		
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 9 (22.22%)	3 / 16 (18.75%)		
occurrences (all)	11	10		
Protein total decreased				

subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)		
occurrences (all)	1	1		
Weight decreased				
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)		
occurrences (all)	4	0		
Blood immunoglobulin G decreased				
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Immunoglobulins decreased				
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)		
occurrences (all)	1	3		
International normalised ratio increased				
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)		
occurrences (all)	1	1		
Blood potassium increased				
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Blood potassium decreased				
subjects affected / exposed	1 / 9 (11.11%)	3 / 16 (18.75%)		
occurrences (all)	4	5		
Body temperature increased				
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Blood creatine increased				
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)		
occurrences (all)	5	0		
Blood creatinine increased				
subjects affected / exposed	3 / 9 (33.33%)	3 / 16 (18.75%)		
occurrences (all)	12	12		
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)		
occurrences (all)	1	2		
Hepatic enzyme increased				

subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	8	
Lipase increased			
subjects affected / exposed	2 / 9 (22.22%)	0 / 16 (0.00%)	
occurrences (all)	12	0	
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Lymphocyte count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Blood magnesium decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Monoclonal immunoglobulin present			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	3	
Sensory level abnormal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Staphylococcus test positive			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	16	
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation feet			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	3 / 9 (33.33%)	0 / 16 (0.00%)	
occurrences (all)	6	0	
Dysgeusia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Paresis			

subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Polyneuropathy			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Transient ischaemic attack			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 9 (22.22%)	7 / 16 (43.75%)	
occurrences (all)	18	19	
Granulocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	10	
Splenic infarction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	1 / 9 (11.11%)	4 / 16 (25.00%)	
occurrences (all)	1	6	
Lymphadenopathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

Monocytosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	2 / 9 (22.22%)	3 / 16 (18.75%)	
occurrences (all)	2	11	
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye disorders			
Erythema of eyelid			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Chronic gastritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)	1 / 16 (6.25%)	
occurrences (all)	13	3	
Diverticular perforation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	2 / 9 (22.22%)	4 / 16 (25.00%)	
occurrences (all)	4	4	
Mucosal inflammation oral			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastric disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastric mucosa erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	1 / 9 (11.11%)	4 / 16 (25.00%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pancreatitis acute			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oral mucosal erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Stomatitis			

subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	4 / 9 (44.44%)	5 / 16 (31.25%)	
occurrences (all)	6	9	
Tongue coated			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Cholecystitis chronic			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 9 (22.22%)	3 / 16 (18.75%)	
occurrences (all)	3	3	
Erythema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin atrophy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin fissures			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin hyperpigmentation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Sensitive skin			

subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Papule			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Penile ulceration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	2	2	
stasis dermatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Renal failure			
subjects affected / exposed	2 / 9 (22.22%)	6 / 16 (37.50%)	
occurrences (all)	3	9	
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Protein urine present			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hyperthyroidism			

subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Muscular weakness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 9 (22.22%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	3	
Bacteriuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Bronchitis viral			

subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Epstein-Barr virus infection			
subjects affected / exposed	4 / 9 (44.44%)	6 / 16 (37.50%)	
occurrences (all)	7	11	
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	4 / 9 (44.44%)	6 / 16 (37.50%)	
occurrences (all)	8	8	
Hepatitis infectious mononucleosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Enteritis infectious			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Catheter site infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oral candidiasis			

subjects affected / exposed	1 / 9 (11.11%)	5 / 16 (31.25%)	
occurrences (all)	1	6	
Parvovirus B19 infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	3	
Systemic mycosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cytomegalovirus infection			
subjects affected / exposed	3 / 9 (33.33%)	10 / 16 (62.50%)	
occurrences (all)	3	20	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Dehydration			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	

Folate deficiency			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Haemosiderosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	5	1	
Hyperglycaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Hyperuricaemia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Vitamin B12 deficiency			
subjects affected / exposed	3 / 9 (33.33%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 9 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2016	Clarification of preexisting safety endpoints, changes in forbidden/permitted concomitant medication, additional blood samples for immunomonitoring and Determination of viral load

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small number of subjects recruited Limits informative value of results

Notes: