Clinical trial results:
A multi-center, randomized, double-blind, placebo controlled, study to evaluate the efficacy and safety of CSJ148 compared to placebo to prevent human cytomegalovirus (HCMV) replication in stem cell transplant patients

Summary

EudraCT number	2014-002150-39
Trial protocol	DE BE
Global end of trial date	07 December 2016

Results information

Result version number	v1 (current)
This version publication date	23 December 2017
First version publication date	23 December 2017

Trial information

Trial identification

Sponsor protocol code	CCSJ148X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268526
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	07 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of CSJ148 on preventing active HCMV infection during the first 98 days after stem cell transplant. To assess the safety and tolerability of CSJ148 when administered to stem cell transplant recipients

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2015
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	Belgium: 12
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 13
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	86
EEA total number of subjects	20

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)	70
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Cohort 1: Six patients were planned for enrollment; 6 patients were enrolled. Cohort 2: Eighty patients were planned and 80 were enrolled.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: CSJ148

Arm description:

Cohort 1: CSJ148 IV q 4weeks

Arm type	Experimental
Investigational medicinal product name	CSJ148
Investigational medicinal product code	CSJ148
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CSJ148 IV infusion every 28 days (days 1, 29, 57 and 85)

Arm title	Cohort 2: CSJ148

Arm description:

Cohort 2: CSJ148 IV q 4weeks

Arm type	Experimental
Investigational medicinal product name	CSJ148
Investigational medicinal product code	CSJ148
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CSJ148 IV infusion every 28 days (days 1, 29, 57 and 85)

Arm title	Cohort 2: Placebo

Arm description:

Cohort 2: Placebo IV q 4weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	CSJ148
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to match CSJ148 IV infusion every 28 days (days 1, 29, 57 and 85)

Number of subjects in period 1	Cohort 1: CSJ148	Cohort 2: CSJ148	Cohort 2: Placebo
Started	6	59	21
PD analysis set (Cohort 2)	0 [1]	42	17
Completed	5	38	16
Not completed	1	21	5
Adverse event, serious fatal	1	11	-
Physician decision	-	-	1
Adverse event, non-fatal	-	2	1
protocol deviation	-	1	-
Subject/guardian decision	-	7	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number is correct as recorded.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: CSJ148
Reporting group description:	
Cohort 1: CSJ148 IV q 4weeks	
Reporting group title	Cohort 2: CSJ148
Reporting group description:	
Cohort 2: CSJ148 IV q 4weeks	
Reporting group title	Cohort 2: Placebo
Reporting group description:	
Cohort 2: Placebo IV q 4weeks	

Reporting group values	Cohort 1: CSJ148	Cohort 2: CSJ148	Cohort 2: Placebo
Number of subjects	6	59	21
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	44	20
From 65-84 years	0	15	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	52.8	54.7	46.0
standard deviation	± 8.70	± 12.33	± 14.33
Gender, Male/Female Units: Subjects			
Female	2	23	6
Male	4	36	15

Reporting group values	Total		
Number of subjects	86		
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)	70		

From 65-84 years	16		
85 years and over	0		

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	31		
Male	55		

Subject analysis sets

Subject analysis set title	Total CSJ148 (Cohort 1 & Cohort 2)
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort 1: CSJ148 IV q 4weeks and Cohort 2: CSJ148 IV q 4weeks

Subject analysis set title	Total CSJ148 (Cohort 1 & Cohort 2)
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort 1: CSJ148 IV q 4weeks and Cohort 2: CSJ148 IV q 4weeks

Reporting group values	Total CSJ148 (Cohort 1 & Cohort 2)	Total CSJ148 (Cohort 1 & Cohort 2)	
Number of subjects	65	65	
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	15	15	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	
Gender, Male/Female			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Cohort 1: CSJ148
Reporting group description: Cohort 1: CSJ148 IV q 4weeks	
Reporting group title	Cohort 2: CSJ148
Reporting group description: Cohort 2: CSJ148 IV q 4weeks	
Reporting group title	Cohort 2: Placebo
Reporting group description: Cohort 2: Placebo IV q 4weeks	
Subject analysis set title	Total CSJ148 (Cohort 1 & Cohort 2)
Subject analysis set type	Full analysis
Subject analysis set description: Cohort 1: CSJ148 IV q 4weeks and Cohort 2: CSJ148 IV q 4weeks	
Subject analysis set title	Total CSJ148 (Cohort 1 & Cohort 2)
Subject analysis set type	Full analysis
Subject analysis set description: Cohort 1: CSJ148 IV q 4weeks and Cohort 2: CSJ148 IV q 4weeks	

Primary: Number of participants who require preemptive HCMV therapy

End point title	Number of participants who require preemptive HCMV

End point description:

Number of participants who require preemptive HCMV therapy. The definition of requiring preemptive anti-HCMV therapy was meeting either one of the following conditions: 1. the plasma HCMV DNA level is >= 1000 copies/mL (with or without HCMV disease) or 2. the plasma HCMV DNA level is < 1000 copies/mL, but HCMV disease was reported

End point type	Primary

End point timeframe:

98 days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The number is correct as recorded.

End point values	Cohort 2: CSJ148	Cohort 2: Placebo	Total CSJ148 (Cohort 1 & Cohort 2)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	59	21	65	
Units: participants	23	9	24	

Statistical analyses

Statistical analysis title	Participants who require preemptive HCMV therapy
Comparison groups	Cohort 2: Placebo v Total CSJ148 (Cohort 1 & Cohort 2)

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.891
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.606
upper limit	1.305

Statistical analysis title	Participants who require preemptive HCMV therapy
Comparison groups	Cohort 2: CSJ148 v Cohort 2: Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.941
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.639
upper limit	1.377

Primary: Number of participants with adverse events as a measure of safety and tolerability

End point title	Number of participants with adverse events as a measure of safety and tolerability[2][3]

End point description:

Number of participants with adverse events as a measure of safety and tolerability. Patients treated with CSJ148 in Cohorts 1 and 2 were pooled to simplify the safety analyses. As this is summary of safety there is no statistical analysis for this primary outcome.

End point type	Primary

End point timeframe:

98 days

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: As this is summary of safety there is no statistical analysis for this primary outcome.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The number is correct as recorded.

End point values	Cohort 2: Placebo	Total CSJ148 (Cohort 1 & Cohort 2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	65		
Units: participants				
At least one treatment-emergent AE	21	65		
At least one drug-related AE	2	0		
At least one SAE	15	46		
At least one drug-related SAE	1	0		
Deaths	0	12		
At least 1 treatment-emergent AE grade 3 or higher	17	58		
Total deaths:those reported after study completion	3	19		
Discontinued study treatment due to any AE	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to start of preemptive HCMV therapy Cohort 2

End point title	Time to start of preemptive HCMV therapy Cohort 2[4]

End point description:

The time to start preemptive therapy is defined as the number of days between initial dose of study drug and the earlier of (1) the start of preemptive therapy, and (2) the development of HCMV disease or death due to HCMV disease, or (3) censored at the EoT visit if no therapy required for Cohort 2

End point type	Secondary

End point timeframe:

98 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The number is correct as recorded.

End point values	Cohort 2: CSJ148	Cohort 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	17		
Units: days				
arithmetic mean (standard deviation)	62.03 (± 12.145)	49.54 (± 13.470)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of times that preemptive HCMV therapy is required -Cohort 2

End point title	Number of times that preemptive HCMV therapy is required -

	Cohort 2[5]

End point description:

Among those who required preemptive therapy, the number of times preemptive therapy was required. (Cohort 2)

End point type	Secondary

End point timeframe:

98 days

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The number is correct as recorded.

End point values	Cohort 2: CSJ148	Cohort 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	17		
Units: number of times				
least squares mean (confidence interval 90%)	2.070 (1.369 to 3.130)	2.540 (1.342 to 4.806)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants developing HCMV disease

End point title	Proportion of participants developing HCMV disease[6]

End point description:

Proportion of participants developing HCMV disease

End point type	Secondary

End point timeframe:

98 days

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The number is correct as recorded.

End point values	Cohort 2: CSJ148	Cohort 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	17		
Units: proportion of participants				
number (confidence interval 90%)	0.119 (0.048 to 0.234)	0 (0 to 0.162)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the serum concentration-time curve during the dosing

interval (AUCtau) for CSJ148 only	
End point title	Area under the serum concentration-time curve during the dosing interval (AUCtau) for CSJ148 only

End point description:

PK parameters were calculated from plasma concentration-time data using non-compartmental methods. The AUCtau was calculated using a linear trapezoidal method

End point type	Secondary

End point timeframe:

Day 1, Day 29, Day 57, Day 85

End point values	Total CSJ148 (Cohort 1 & Cohort 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: day*ug/mL				
arithmetic mean (standard deviation)				
Day 1	7310 (± 2310)			
Day 29	9890 (± 3470)			
Day 57	11400 (± 4020)			
Day 85	12900 (± 4380)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum serum concentration during the dosing interval (Cmax) for CSJ148 only	
End point title	Maximum serum concentration during the dosing interval (Cmax) for CSJ148 only

End point description:

Cmax is the observed maximum plasma (or serum or blood) concentration following drug administration [ug / mL] for CSJ148 only

End point type	Secondary

End point timeframe:

Day 1, Day 29, Day 57, Day 85

End point values	Total CSJ148 (Cohort 1 & Cohort 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: ug/mL				
arithmetic mean (standard deviation)				

Day 1	1040 (± 356)			
Day 29	1100 (± 282)			
Day 57	1180 (± 316)			
Day 85	1230 (± 458)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough serum concentration (Ctrough) for CSJ148 only

End point title	Trough serum concentration (Ctrough) for CSJ148 only

End point description:

Ctrough is The observed plasma (or serum or blood) concentration at the end of a drug administration dosing interval [ug / mL]

End point type	Secondary

End point timeframe:

Day 1, Day 29, Day 57, Day 85

End point values	Total CSJ148 (Cohort 1 & Cohort 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: ug/mL				
arithmetic mean (standard deviation)				
Day 1	104 (± 59.7)			
Day 29	167 (± 85.5)			
Day 57	214 (± 152)			
Day 85	223 (± 104)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation ratio(Racc) for CSJ148 only at Day 85

End point title	Accumulation ratio(Racc) for CSJ148 only at Day 85

End point description:

Accumulation ratio(Racc) is Racc: Accumulation ratio, calculated by AUCtau (Day 85) divided by AUCtau (for the 1st dose).

End point type	Secondary

End point timeframe:

Day 1 and Day 85

End point values	Total CSJ148 (Cohort 1 & Cohort 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: Ratio				
arithmetic mean (standard deviation)	1.83 (± 0.531)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (T1/2) for CSJ148 only at Day 85

End point title	Half-life (T1/2) for CSJ148 only at Day 85
End point description:	
T1/2 is the terminal elimination half-life [time]	
End point type	Secondary
End point timeframe:	
Day 1 and Day 85	

End point values	Total CSJ148 (Cohort 1 & Cohort 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: day				
arithmetic mean (standard deviation)	19.7 (± 7.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lambda_z for CSJ148 only at Day 85

End point title	Lambda_z for CSJ148 only at Day 85
End point description:	
Lambda_z is the terminal elimination rate constant [1/day] at Day 85	
End point type	Secondary
End point timeframe:	
Day 1 and Day 85	

End point values	Total CSJ148 (Cohort 1 & Cohort 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: 1/day				
arithmetic mean (standard deviation)	0.0409 (± 0.0175)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Novartis has reported the SAE field"# of deaths resulting from AEs" all those deaths,resulting from SAEs deemed to be causally related to treatment by the investigator. Additional deaths: 2 in placebo during follow-up (Day 100-183) after early treatment/study discontinuation. 1 in placebo and 7 in CSJ148 post end of study (Day 183).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Total CSJ148

Reporting group description:

Total CSJ148

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Total CSJ148	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 65 (70.77%)	15 / 21 (71.43%)	
number of deaths (all causes)	12	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic myeloid leukaemia recurrent			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic myelomonocytic leukaemia			

subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 65 (1.54%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer recurrent			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma recurrent			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	3 / 65 (4.62%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 65 (3.08%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	9 / 65 (13.85%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute graft versus host disease in liver			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 65 (1.54%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic graft versus host disease in liver			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			

subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 65 (4.62%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 65 (3.08%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 65 (1.54%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus test positive			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Engraft failure			

subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac mass			

subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (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			
Facial paresis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	8 / 65 (12.31%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 13	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic lesion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis erosive			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 65 (3.08%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal lesion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic lesion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (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	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteriuria			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cytomegalovirus colitis			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastritis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	2 / 65 (3.08%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis tuberculous			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (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	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human herpesvirus 6 infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JC virus infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 65 (1.54%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			

subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 65 (4.62%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (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	2 / 65 (3.08%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 65 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Total CSJ148	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 65 (100.00%)	21 / 21 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 65 (35.38%)	5 / 21 (23.81%)	
occurrences (all)	25	5	
Hypotension			
subjects affected / exposed	9 / 65 (13.85%)	4 / 21 (19.05%)	
occurrences (all)	12	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 65 (10.77%)	2 / 21 (9.52%)	
occurrences (all)	7	2	
Catheter site erythema			

subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Catheter site pain			
subjects affected / exposed	6 / 65 (9.23%)	1 / 21 (4.76%)	
occurrences (all)	6	3	
Chest discomfort			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Chills			
subjects affected / exposed	15 / 65 (23.08%)	4 / 21 (19.05%)	
occurrences (all)	20	4	
Fatigue			
subjects affected / exposed	18 / 65 (27.69%)	7 / 21 (33.33%)	
occurrences (all)	23	7	
Generalised oedema			
subjects affected / exposed	7 / 65 (10.77%)	0 / 21 (0.00%)	
occurrences (all)	9	0	
Non-cardiac chest pain			
subjects affected / exposed	8 / 65 (12.31%)	1 / 21 (4.76%)	
occurrences (all)	10	1	
Oedema peripheral			
subjects affected / exposed	12 / 65 (18.46%)	2 / 21 (9.52%)	
occurrences (all)	15	4	
Pain			
subjects affected / exposed	6 / 65 (9.23%)	0 / 21 (0.00%)	
occurrences (all)	7	0	
Pyrexia			
subjects affected / exposed	38 / 65 (58.46%)	10 / 21 (47.62%)	
occurrences (all)	56	14	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	10 / 65 (15.38%)	3 / 21 (14.29%)	
occurrences (all)	10	4	
Acute graft versus host disease in intestine			

subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Acute graft versus host disease in skin			
subjects affected / exposed	14 / 65 (21.54%)	3 / 21 (14.29%)	
occurrences (all)	16	3	
Chronic graft versus host disease			
subjects affected / exposed	6 / 65 (9.23%)	4 / 21 (19.05%)	
occurrences (all)	7	5	
Chronic graft versus host disease in skin			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 65 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 65 (38.46%)	9 / 21 (42.86%)	
occurrences (all)	29	10	
Dyspnoea			
subjects affected / exposed	13 / 65 (20.00%)	3 / 21 (14.29%)	
occurrences (all)	14	3	
Epistaxis			
subjects affected / exposed	8 / 65 (12.31%)	2 / 21 (9.52%)	
occurrences (all)	14	2	
Haemoptysis			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	7	0	
Hiccups			
subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Hypoxia			
subjects affected / exposed	7 / 65 (10.77%)	0 / 21 (0.00%)	
occurrences (all)	9	0	

Nasal congestion			
subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Oropharyngeal pain			
subjects affected / exposed	12 / 65 (18.46%)	3 / 21 (14.29%)	
occurrences (all)	12	3	
Pharyngeal inflammation			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Pleural effusion			
subjects affected / exposed	9 / 65 (13.85%)	1 / 21 (4.76%)	
occurrences (all)	9	1	
Productive cough			
subjects affected / exposed	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Rhinorrhoea			
subjects affected / exposed	3 / 65 (4.62%)	3 / 21 (14.29%)	
occurrences (all)	4	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 65 (7.69%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Confusional state			
subjects affected / exposed	7 / 65 (10.77%)	0 / 21 (0.00%)	
occurrences (all)	8	0	
Hallucination			
subjects affected / exposed	5 / 65 (7.69%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Insomnia			
subjects affected / exposed	15 / 65 (23.08%)	6 / 21 (28.57%)	
occurrences (all)	15	7	
Sleep disorder			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	5 / 65 (7.69%)	2 / 21 (9.52%)	
occurrences (all)	5	2	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Blood bilirubin increased			
subjects affected / exposed	7 / 65 (10.77%)	1 / 21 (4.76%)	
occurrences (all)	7	2	
Blood creatinine increased			
subjects affected / exposed	8 / 65 (12.31%)	3 / 21 (14.29%)	
occurrences (all)	9	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 65 (9.23%)	0 / 21 (0.00%)	
occurrences (all)	6	0	
Skin abrasion			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Transfusion reaction			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	8 / 65 (12.31%)	2 / 21 (9.52%)	
occurrences (all)	8	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 65 (24.62%)	3 / 21 (14.29%)	
occurrences (all)	18	3	
Headache			
subjects affected / exposed	24 / 65 (36.92%)	6 / 21 (28.57%)	
occurrences (all)	33	6	
Neuropathy peripheral			
subjects affected / exposed	6 / 65 (9.23%)	1 / 21 (4.76%)	
occurrences (all)	6	1	

Syncope			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Tremor			
subjects affected / exposed	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 65 (9.23%)	4 / 21 (19.05%)	
occurrences (all)	10	5	
Febrile neutropenia			
subjects affected / exposed	25 / 65 (38.46%)	10 / 21 (47.62%)	
occurrences (all)	30	11	
Neutropenia			
subjects affected / exposed	6 / 65 (9.23%)	5 / 21 (23.81%)	
occurrences (all)	10	6	
Thrombocytopenia			
subjects affected / exposed	9 / 65 (13.85%)	3 / 21 (14.29%)	
occurrences (all)	11	5	
Eye disorders			
Dry eye			
subjects affected / exposed	14 / 65 (21.54%)	5 / 21 (23.81%)	
occurrences (all)	15	6	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	6 / 65 (9.23%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Abdominal distension			
subjects affected / exposed	6 / 65 (9.23%)	3 / 21 (14.29%)	
occurrences (all)	8	3	
Abdominal pain			
subjects affected / exposed	16 / 65 (24.62%)	5 / 21 (23.81%)	
occurrences (all)	19	5	
Abdominal pain upper			
subjects affected / exposed	5 / 65 (7.69%)	5 / 21 (23.81%)	
occurrences (all)	5	5	
Constipation			

subjects affected / exposed	19 / 65 (29.23%)	8 / 21 (38.10%)	
occurrences (all)	23	9	
Diarrhoea			
subjects affected / exposed	43 / 65 (66.15%)	12 / 21 (57.14%)	
occurrences (all)	66	19	
Dry mouth			
subjects affected / exposed	11 / 65 (16.92%)	3 / 21 (14.29%)	
occurrences (all)	13	3	
Dyspepsia			
subjects affected / exposed	7 / 65 (10.77%)	3 / 21 (14.29%)	
occurrences (all)	7	3	
Epigastric discomfort			
subjects affected / exposed	2 / 65 (3.08%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Gastrointestinal inflammation			
subjects affected / exposed	8 / 65 (12.31%)	0 / 21 (0.00%)	
occurrences (all)	8	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 65 (9.23%)	0 / 21 (0.00%)	
occurrences (all)	7	0	
Haemorrhoids			
subjects affected / exposed	13 / 65 (20.00%)	2 / 21 (9.52%)	
occurrences (all)	13	2	
Lip dry			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Melaena			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	6	0	
Mouth haemorrhage			
subjects affected / exposed	3 / 65 (4.62%)	2 / 21 (9.52%)	
occurrences (all)	3	2	
Nausea			
subjects affected / exposed	45 / 65 (69.23%)	14 / 21 (66.67%)	
occurrences (all)	66	19	
Oesophagitis			

subjects affected / exposed	9 / 65 (13.85%)	1 / 21 (4.76%)	
occurrences (all)	9	1	
Stomatitis			
subjects affected / exposed	36 / 65 (55.38%)	15 / 21 (71.43%)	
occurrences (all)	43	17	
Tongue ulceration			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	38 / 65 (58.46%)	14 / 21 (66.67%)	
occurrences (all)	59	17	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences (all)	4	4	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Decubitus ulcer			
subjects affected / exposed	5 / 65 (7.69%)	0 / 21 (0.00%)	
occurrences (all)	6	0	
Dry skin			
subjects affected / exposed	6 / 65 (9.23%)	4 / 21 (19.05%)	
occurrences (all)	7	4	
Eczema			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Erythema			
subjects affected / exposed	4 / 65 (6.15%)	3 / 21 (14.29%)	
occurrences (all)	5	5	
Petechiae			
subjects affected / exposed	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Pruritus			

subjects affected / exposed	18 / 65 (27.69%)	4 / 21 (19.05%)	
occurrences (all)	25	6	
Rash			
subjects affected / exposed	24 / 65 (36.92%)	7 / 21 (33.33%)	
occurrences (all)	29	7	
Rash generalised			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Rash macular			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Urticaria			
subjects affected / exposed	6 / 65 (9.23%)	2 / 21 (9.52%)	
occurrences (all)	8	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Chronic kidney disease			
subjects affected / exposed	0 / 65 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Dysuria			
subjects affected / exposed	5 / 65 (7.69%)	2 / 21 (9.52%)	
occurrences (all)	6	2	
Haematuria			
subjects affected / exposed	10 / 65 (15.38%)	1 / 21 (4.76%)	
occurrences (all)	11	1	
Pollakiuria			
subjects affected / exposed	8 / 65 (12.31%)	2 / 21 (9.52%)	
occurrences (all)	8	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 65 (18.46%)	1 / 21 (4.76%)	
occurrences (all)	13	1	
Back pain			

subjects affected / exposed	17 / 65 (26.15%)	5 / 21 (23.81%)	
occurrences (all)	19	5	
Bone pain			
subjects affected / exposed	9 / 65 (13.85%)	1 / 21 (4.76%)	
occurrences (all)	11	1	
Musculoskeletal pain			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Myalgia			
subjects affected / exposed	7 / 65 (10.77%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Pain in extremity			
subjects affected / exposed	5 / 65 (7.69%)	2 / 21 (9.52%)	
occurrences (all)	5	4	
Infections and infestations			
Candida infection			
subjects affected / exposed	5 / 65 (7.69%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Clostridium difficile infection			
subjects affected / exposed	5 / 65 (7.69%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Device related infection			
subjects affected / exposed	3 / 65 (4.62%)	2 / 21 (9.52%)	
occurrences (all)	3	2	
Folliculitis			
subjects affected / exposed	7 / 65 (10.77%)	2 / 21 (9.52%)	
occurrences (all)	8	2	
Herpes zoster			
subjects affected / exposed	4 / 65 (6.15%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Human herpesvirus 6 infection			
subjects affected / exposed	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Oral candidiasis			
subjects affected / exposed	5 / 65 (7.69%)	3 / 21 (14.29%)	
occurrences (all)	5	3	

Oral herpes			
subjects affected / exposed	4 / 65 (6.15%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Papilloma viral infection			
subjects affected / exposed	0 / 65 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	4 / 65 (6.15%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Rhinovirus infection			
subjects affected / exposed	1 / 65 (1.54%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Staphylococcal bacteraemia			
subjects affected / exposed	5 / 65 (7.69%)	3 / 21 (14.29%)	
occurrences (all)	5	3	
Upper respiratory tract infection			
subjects affected / exposed	8 / 65 (12.31%)	4 / 21 (19.05%)	
occurrences (all)	8	4	
Urinary tract infection			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	10	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	27 / 65 (41.54%)	7 / 21 (33.33%)	
occurrences (all)	33	8	
Fluid overload			
subjects affected / exposed	5 / 65 (7.69%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Hyperglycaemia			
subjects affected / exposed	8 / 65 (12.31%)	1 / 21 (4.76%)	
occurrences (all)	8	1	
Hyperkalaemia			
subjects affected / exposed	6 / 65 (9.23%)	1 / 21 (4.76%)	
occurrences (all)	8	1	
Hypocalcaemia			

subjects affected / exposed	7 / 65 (10.77%)	1 / 21 (4.76%)	
occurrences (all)	9	1	
Hypokalaemia			
subjects affected / exposed	20 / 65 (30.77%)	5 / 21 (23.81%)	
occurrences (all)	27	5	
Hypomagnesaemia			
subjects affected / exposed	9 / 65 (13.85%)	4 / 21 (19.05%)	
occurrences (all)	10	4	
Hypophosphataemia			
subjects affected / exposed	6 / 65 (9.23%)	3 / 21 (14.29%)	
occurrences (all)	10	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2014	Amendment 1 introduced the following changes: 1) New weight inclusion criterion to comply with the WHO limit for total human exposure to DNA (< 10ng/dose). Based on the DNA content of the current formulation and limitations of the current purification process, an upper body weight of 120 kg is the maximum permitted to comply with the total human exposure and allow for minor variability in the residual DNA content of the formulation. 2) Other changes made included those that facilitated the execution of the trial, added safety data from the first-in-human study CCSJ148X2101, and made administrative modifications and corrected typographical errors.
12 August 2015	Amendment 2 introduced the following changes: 1) Modified the PK collection time points at 120 minutes and 132 minutes post dose to one PK time point at 3 hour in order to allow all blood draws to be taken from a central catheter and not from direct venipuncture. 2) Increased the threshold for exclusion of severe liver injury. Liver abnormalities are not expected toxicities based on the type of compound (mAb), pre-clinical and first in human data. Additionally, many patients have mildly elevated liver function tests (LFTs) at screening (around 3 ULN) and go ahead Hematopoietic Stem Cell Transplantation (HSCT) procedure. Appendix 2 (Liver event definitions and follow up) was eliminated. 3) Other changes made included those that facilitated the execution of the trial, added safety data from the first-in-human study CCSJ148X2101, and made administrative modifications and corrected typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported