Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seronegative Kidney Transplant Recipients Receiving an Organ from a CMV-Seropositive Donor

Summary

EudraCT number	2013-000464-29
Trial protocol	DE ES
Global end of trial date	05 November 2020

Results information

Result version number	v3 (current)
This version publication date	13 February 2022
First version publication date	29 April 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	0113-CL-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01974206
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Transparency, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Transparency, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com

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	05 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate efficacy and safety of ASP0113 compared to placebo in reducing the incidence of Cytomegalovirus (CMV) viremia through 1 year post first study drug injection in CMV-seronegative participants who received a kidney from a CMV-seropositive donor.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

In the first 10 days after the transplant, patients received prophylactic valganciclovir or ganciclovir (dose per package insert) from the day of randomization to prevent Cytomegalovirus (CMV) disease. After randomization, patients continued to receive valganciclovir or ganciclovir until 100 days post-transplant. Valganciclovir or ganciclovir could be interrupted, dose adjusted or replaced by other CMV-specific antiviral prophylaxis (AVP) per standard of care after the day of randomization.

Evidence for comparator: -

Actual start date of recruitment	20 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 93
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	150
EEA total number of subjects	39

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)	129
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 150 participants were enrolled into the study from 6 countries. Eligible participants were ≥18 years of age, CMV-seronegative at the time of the transplant and had a kidney allograft from a CMV-seropositive living or deceased donor. After the primary period completion, 149 participants entered the long-term follow-up period.

Pre-assignment

Screening details:

Screening assessments were performed from 14-30 days after the transplant. Patients were randomized at day 30, in relation to the day of the transplant, in a 1:1 ratio to ASP0113 or placebo. Participants were stratified by the use of antithymocyte globulin (ATG) prior to randomization and by the receipt of a kidney from a living or deceased donor.

Period 1

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

Blinding implementation details:

This was a double-blind study. Participants were randomized to receive ASP0113 or placebo in a double-blind fashion such that the investigator, sponsor’s study management team, clinical staff nor the participant knew which agent was being administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received 1 mL of 5 mg/mL of placebo via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received Placebo in 2-mL vials containing phosphate-buffered saline.

Arm title	ASP0113 5mg

Arm description:

Participants received 1 mL of 5 mg/mL of ASP0113 via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).

Arm type	Experimental
Investigational medicinal product name	ASP0113
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received ASP0113 in single dose 2-ml vials containing 1.3 ml of 5 mg/mL of ASP0113.

Number of subjects in period 1	Placebo	ASP0113 5mg
Started	74	76
Received Treatment	74	75
Completed	68	75
Not completed	6	1
Consent withdrawn by subject	3	-
Physician decision	1	-
Patient did not take study drug	-	1
Death	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received 1 mL of 5 mg/mL of placebo via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).	
Reporting group title	ASP0113 5mg
Reporting group description:	
Participants received 1 mL of 5 mg/mL of ASP0113 via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).	

Reporting group values	Placebo	ASP0113 5mg	Total
Number of subjects	74	76	150
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.9	50.8	
standard deviation	± 13.3	± 13.6	-
Gender categorical Units: Participants			
Male	55	55	110
Female	19	21	40
Ethnicity Units: Subjects			
Hispanic or Latino	2	70	72
Not Hispanic or Latino	72	6	78
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	14	11	25
White	57	61	118
More than one race	0	0	0
Unknown or Not Reported	2	4	6
Use of ATG Units: Subjects			
Use of ATG = No	44	44	88
Use of ATG = Yes	30	32	62
Source of Current Transplant Units: Subjects			
Living Unrelated Donor	10	17	27
Living Related Donor	16	9	25
Deceased Donor	48	49	97

Not Recorded	0	1	1
Randomization Strata Units: Subjects			
Living Donor & ATG Use = No	18	16	34
Living Donor & ATG Use = Yes	8	10	18
Deceased Donor & ATG Use = Yes	22	22	44
Deceased Donor & ATG Use = No	26	27	53
Not Recorded	0	1	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received 1 mL of 5 mg/mL of placebo via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).	
Reporting group title	ASP0113 5mg
Reporting group description:	
Participants received 1 mL of 5 mg/mL of ASP0113 via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).	

Primary: Percentage of Participants with CMV Viremia Through One Year Post First Study Drug Injection. (Primary Study Period)

End point title	Percentage of Participants with CMV Viremia Through One Year Post First Study Drug Injection. (Primary Study Period)
End point description:	
CMV viremia was defined as presence of cytomegalovirus as measured in plasma viral load of ≥ 1000 IU/mL by central laboratory assay. A participants who discontinued the study without a positive CMV viral load was imputed as having a CMV viremia. A participant who had more than one viral load ≥ 1000 IU/mL by central assay was counted once in this summary. CMV viral loads after first injection (Day 1) through Day 380 (scheduled or unscheduled) were included in the analysis. The analysis population was the Full Analysis Set (FAS) which consisted of all randomized patients who received at least 1 dose of randomized study drug and who had at least 1 post dose viral load assessment within 1 year post first injection by central laboratory.	
End point type	Primary
End point timeframe:	
From first study dose injection (Day 1) up to one year post study drug injection (up to Day 380)	

End point values	Placebo	ASP0113 5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: Percentage of Participants				
number (not applicable)				
Known CMV Viremia	35.6	35.6		
Imputed CMV Viremia Due to Discontinuation	5.5	0		

Statistical analyses

Statistical analysis title	Common Odds Ratio for Patients With CMV
Statistical analysis description:	
The Cochran-Mantel-Haenszel (CMH) estimate of the common odds ratio (ASP0113 vs placebo) stratified by randomization strata, and the 90% CIs of the CMH odds ratio stratified by randomization group.	
Comparison groups	Placebo v ASP0113 5mg

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.307 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	0.79
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.43
upper limit	1.47

Notes:

[1] - P-value (1-sided) of the CMH adjusted odds ratio stratified by randomization group.

Secondary: Percentage of Participants with Adjudicated CMV-Associated Disease, Including CMV Syndrome and CMV Tissue-Invasive Disease (Primary Study Period)

End point title	Percentage of Participants with Adjudicated CMV-Associated Disease, Including CMV Syndrome and CMV Tissue-Invasive Disease (Primary Study Period)

End point description:

An independent panel of medical experts reviewed/adjudicated events of CMV-associated disease including CMV syndrome and tissue invasive disease, which were defined according to the American Society of Transplantation Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation 2006. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

From first study dose injection (Day 1) up to one year post study drug injection (up to Day 380)

End point values	Placebo	ASP0113 5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: Percentage of Participants				
number (not applicable)	19.18	19.18		

Statistical analyses

Statistical analysis title	Common Odds Ratio for CMV-Associated Disease

Statistical analysis description:

The exact Cochran-Mantel-Haenszel (CMH) estimate of the common odds ratio (ASP0113 vs placebo) stratified by randomization group, and the 90% CI of the exact CMH odds ratio stratified by randomization group.

Comparison groups	Placebo v ASP0113 5mg

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.576 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.46
upper limit	2.15

Notes:

[2] - P-value (1-sided) of the exact CMH method adjusted odds ratio stratified by randomization group.

Secondary: Percentage of Participants with CMV Viremia Defined as Plasma Viral Load ≥ the Lower Limit of Quantification (LLOQ) Assessed by Central Laboratory (Primary Study Period)

End point title	Percentage of Participants with CMV Viremia Defined as Plasma Viral Load ≥ the Lower Limit of Quantification (LLOQ) Assessed by Central Laboratory (Primary Study Period)

End point description:

The central laboratory had the LLOQ level for CMV viral load assessment. When the viral load was below the LLOQ the actual reading was not possible and was denoted as ≤LLOQ. If the participant had any CMV viral load assessments greater than the LLOQ, set up by the central laboratory, participant was classified as viremic and was included in the analysis. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

From first study dose injection (Day 1) up to one year post study drug injection (up to Day 380)

End point values	Placebo	ASP0113 5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: Percentage of Participants				
number (not applicable)	49.32	46.58		

Statistical analyses

Statistical analysis title	Common Odds Ratio for Participants w/ CMV Viremia

Statistical analysis description:

The exact Cochran-Mantel-Haenszel (CMH) estimate of the common odds ratio (ASP0113 vs placebo) stratified by randomization group, and the 90% CI of the exact CMH odds ratio stratified by randomization group.

Comparison groups	Placebo v ASP0113 5mg

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.408 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.48
upper limit	1.59

Notes:

[3] - P-value (1-sided) of the exact CMH method adjusted odds ratio stratified by randomization group.

Secondary: Percentage of Participants Who Took Adjudicated CMV-specific antiviral therapy (AVT) for the Treatment of CMV Viremia or Disease (Primary Study Period)

End point title	Percentage of Participants Who Took Adjudicated CMV-specific antiviral therapy (AVT) for the Treatment of CMV Viremia or Disease (Primary Study Period)

End point description:

An independent panel of medical experts reviewed/adjudicated events of CMV-specific AVT for treatment of CMV viremia or disease. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

From first study dose injection (Day 1) up to one year post study drug injection (up to Day 380)

End point values	Placebo	ASP0113 5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: Percentage of Participants				
number (not applicable)	45.21	42.47		

Statistical analyses

Statistical analysis title	Common Odds Ratio for Participants With CMV-AVT

Statistical analysis description:

The exact Cochran-Mantel-Haenszel (CMH) estimate of the common odds ratio (ASP0113 vs placebo) stratified by randomization group, and the 90% CI of the exact CMH odds ratio stratified by randomization group.

Comparison groups	Placebo v ASP0113 5mg

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.419 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.48
upper limit	1.61

Notes:

[4] - P-value (1-sided) of the exact CMH method adjusted odds ratio stratified by randomization group.

Secondary: Percentage of Participants with Graft Survival (Primary Study Period)

End point title	Percentage of Participants with Graft Survival (Primary Study Period)

End point description:

Graft survival was defined for any participants that did not fit the definition of graft loss. Graft loss was defined as participant death, re-transplant, nephrectomy, or return to permanent dialysis (i.e., for > 30 days). Missing values for graft survival were not included in the denominator when making the proportion. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

From first study dose injection (Day 1) up to one year post study drug injection (up to Day 380)

End point values	Placebo	ASP0113 5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of Participants				
number (not applicable)	98.53	100		

Statistical analyses

Statistical analysis title	Common Odds Ratio of Participants w/Graft Survival

Statistical analysis description:

Exact Cochran-Mantel-Haenszel estimate of the common odds ratio (ASP0113 versus Placebo) could not be estimated and is denoted as "9999." Moreover, upper limit of 90% CI of oods ratio is an infinity value and is also denoted as "9999."

Comparison groups	Placebo v ASP0113 5mg

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	9999
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.11
upper limit	9999

Notes:

[5] - P-value (1-sided) of the Exact Cochran-Mantel-Haenszel method adjusted odds ratio stratified by randomization group.

Secondary: Percentage of Participants with Graft Survival (Long-term Follow up)

End point title	Percentage of Participants with Graft Survival (Long-term Follow up)

End point description:

Graft survival was defined for any participants that did not fit the definition of graft loss. Graft loss was defined as participant death, re-transplant, nephrectomy, or return to permanent dialysis (i.e., for > 30 days). The analysis population was all participants who entered long-term follow-up.

End point type	Secondary

End point timeframe:

Month 18, 30, 42, 54, and 66

End point values	Placebo	ASP0113 5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of participants				
number (not applicable)				
Long-term Follow up Month 18	91.9	94.7		
Long-term Follow up Month 30	83.8	81.6		
Long-term Follow up Month 42	85.1	80.3		
Long-term Follow up Month 54	78.4	77.6		
Long-term Follow up Month 66	82.4	84.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 380

Adverse event reporting additional description:

Treatment Emergent Adverse Event (TEAE) was defined as an AE observed after the first study drug injection Day 1 through Day 380. No AEs were collected/reported during the long-term follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v16

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received 1 mL of 5 mg/mL of placebo via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).

Reporting group title	ASP0113

Reporting group description:

Participants received 1 mL of 5 mg/mL of ASP0113 via injection in the deltoid muscle alternating sides with each dose on days 30, 60, 90, 120 and 180 in relation to the day of transplant (Day 0).

Serious adverse events	Placebo	ASP0113	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 74 (48.65%)	44 / 75 (58.67%)	
number of deaths (all causes)	5	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			

subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ureteral stent removal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral prostatectomy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	3 / 74 (4.05%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	4 / 74 (5.41%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 74 (5.41%)	5 / 75 (6.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HLA marker study positive			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
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			
Bone fissure			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Perinephric collection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 74 (2.70%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 74 (1.35%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
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			
Diabetic foot			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephropathy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	6 / 74 (8.11%)	10 / 75 (13.33%)	
occurrences causally related to treatment / all	0 / 10	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder atrophy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism tertiary			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (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			
Rhabdomyolysis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BK virus infection			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacterial pyelonephritis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus mucocutaneous ulcer			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	2 / 74 (2.70%)	7 / 75 (9.33%)	
occurrences causally related to treatment / all	1 / 2	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus oesophagitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences causally related to treatment / all	1 / 3	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus syndrome			
subjects affected / exposed	5 / 74 (6.76%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	3 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			

subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr viraemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	2 / 74 (2.70%)	5 / 75 (6.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia cytomegaloviral			

subjects affected / exposed	0 / 74 (0.00%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyomavirus-associated nephropathy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			

subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (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 / 74 (2.70%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 74 (1.35%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 74 (0.00%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 74 (2.70%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
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	Placebo	ASP0113	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 74 (97.30%)	75 / 75 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 74 (10.81%)	11 / 75 (14.67%)	
occurrences (all)	10	16	
Hypertension			
subjects affected / exposed	9 / 74 (12.16%)	12 / 75 (16.00%)	
occurrences (all)	14	12	
Arteriosclerosis			
subjects affected / exposed	1 / 74 (1.35%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
Orthostatic hypotension			
subjects affected / exposed	4 / 74 (5.41%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
Surgical and medical procedures			
Ureteral stent removal			
subjects affected / exposed	6 / 74 (8.11%)	1 / 75 (1.33%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 74 (10.81%)	5 / 75 (6.67%)	
occurrences (all)	8	5	
Chills			
subjects affected / exposed	4 / 74 (5.41%)	2 / 75 (2.67%)	
occurrences (all)	4	2	
Oedema peripheral			
subjects affected / exposed	5 / 74 (6.76%)	9 / 75 (12.00%)	
occurrences (all)	8	13	
Oedema			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences (all)	3	5	
Injection site pain			

subjects affected / exposed	18 / 74 (24.32%)	47 / 75 (62.67%)	
occurrences (all)	46	277	
Injection site erythema			
subjects affected / exposed	2 / 74 (2.70%)	8 / 75 (10.67%)	
occurrences (all)	2	14	
Fatigue			
subjects affected / exposed	24 / 74 (32.43%)	27 / 75 (36.00%)	
occurrences (all)	38	59	
Pyrexia			
subjects affected / exposed	13 / 74 (17.57%)	9 / 75 (12.00%)	
occurrences (all)	14	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 74 (5.41%)	7 / 75 (9.33%)	
occurrences (all)	4	8	
Oropharyngeal pain			
subjects affected / exposed	5 / 74 (6.76%)	4 / 75 (5.33%)	
occurrences (all)	5	4	
Dyspnoea			
subjects affected / exposed	8 / 74 (10.81%)	5 / 75 (6.67%)	
occurrences (all)	10	9	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 74 (8.11%)	8 / 75 (10.67%)	
occurrences (all)	8	11	
Investigations			
Blood creatinine increased			
subjects affected / exposed	16 / 74 (21.62%)	11 / 75 (14.67%)	
occurrences (all)	19	17	
Weight increased			
subjects affected / exposed	3 / 74 (4.05%)	4 / 75 (5.33%)	
occurrences (all)	3	4	
White blood cell count decreased			
subjects affected / exposed	4 / 74 (5.41%)	1 / 75 (1.33%)	
occurrences (all)	12	1	
Injury, poisoning and procedural complications			

Complications of transplant surgery			
subjects affected / exposed	4 / 74 (5.41%)	2 / 75 (2.67%)	
occurrences (all)	4	2	
Complications of transplanted kidney			
subjects affected / exposed	4 / 74 (5.41%)	4 / 75 (5.33%)	
occurrences (all)	4	4	
Procedural pain			
subjects affected / exposed	2 / 74 (2.70%)	6 / 75 (8.00%)	
occurrences (all)	2	10	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences (all)	3	5	
Bradycardia			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences (all)	3	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 74 (12.16%)	3 / 75 (4.00%)	
occurrences (all)	12	3	
Headache			
subjects affected / exposed	12 / 74 (16.22%)	13 / 75 (17.33%)	
occurrences (all)	14	13	
Tremor			
subjects affected / exposed	7 / 74 (9.46%)	10 / 75 (13.33%)	
occurrences (all)	9	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 74 (5.41%)	7 / 75 (9.33%)	
occurrences (all)	4	7	
Neutropenia			
subjects affected / exposed	6 / 74 (8.11%)	10 / 75 (13.33%)	
occurrences (all)	6	11	
Leukopenia			
subjects affected / exposed	19 / 74 (25.68%)	29 / 75 (38.67%)	
occurrences (all)	23	32	
Thrombocytopenia			

subjects affected / exposed	5 / 74 (6.76%)	1 / 75 (1.33%)	
occurrences (all)	6	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 74 (1.35%)	5 / 75 (6.67%)	
occurrences (all)	1	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 74 (8.11%)	8 / 75 (10.67%)	
occurrences (all)	7	9	
Abdominal pain upper			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences (all)	3	5	
Constipation			
subjects affected / exposed	6 / 74 (8.11%)	4 / 75 (5.33%)	
occurrences (all)	7	4	
Diarrhoea			
subjects affected / exposed	24 / 74 (32.43%)	23 / 75 (30.67%)	
occurrences (all)	38	33	
Dyspepsia			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences (all)	3	6	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 74 (8.11%)	1 / 75 (1.33%)	
occurrences (all)	7	1	
Nausea			
subjects affected / exposed	14 / 74 (18.92%)	13 / 75 (17.33%)	
occurrences (all)	19	22	
Vomiting			
subjects affected / exposed	9 / 74 (12.16%)	9 / 75 (12.00%)	
occurrences (all)	13	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 74 (2.70%)	4 / 75 (5.33%)	
occurrences (all)	2	4	
Alopecia			

subjects affected / exposed	8 / 74 (10.81%)	3 / 75 (4.00%)	
occurrences (all)	9	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	6 / 74 (8.11%)	5 / 75 (6.67%)	
occurrences (all)	6	5	
Haematuria			
subjects affected / exposed	7 / 74 (9.46%)	6 / 75 (8.00%)	
occurrences (all)	7	8	
Kidney fibrosis			
subjects affected / exposed	4 / 74 (5.41%)	7 / 75 (9.33%)	
occurrences (all)	4	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 74 (10.81%)	5 / 75 (6.67%)	
occurrences (all)	10	7	
Musculoskeletal pain			
subjects affected / exposed	2 / 74 (2.70%)	4 / 75 (5.33%)	
occurrences (all)	2	4	
Musculoskeletal discomfort			
subjects affected / exposed	6 / 74 (8.11%)	4 / 75 (5.33%)	
occurrences (all)	7	11	
Muscular weakness			
subjects affected / exposed	4 / 74 (5.41%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
Muscle spasms			
subjects affected / exposed	5 / 74 (6.76%)	3 / 75 (4.00%)	
occurrences (all)	6	3	
Back pain			
subjects affected / exposed	8 / 74 (10.81%)	5 / 75 (6.67%)	
occurrences (all)	9	6	
Myalgia			
subjects affected / exposed	15 / 74 (20.27%)	21 / 75 (28.00%)	
occurrences (all)	22	38	
Pain in extremity			

subjects affected / exposed	8 / 74 (10.81%)	4 / 75 (5.33%)	
occurrences (all)	9	5	
Infections and infestations			
Cytomegalovirus viraemia			
subjects affected / exposed	19 / 74 (25.68%)	22 / 75 (29.33%)	
occurrences (all)	22	30	
Cytomegalovirus syndrome			
subjects affected / exposed	6 / 74 (8.11%)	7 / 75 (9.33%)	
occurrences (all)	6	7	
Cytomegalovirus infection			
subjects affected / exposed	5 / 74 (6.76%)	3 / 75 (4.00%)	
occurrences (all)	7	4	
BK virus infection			
subjects affected / exposed	16 / 74 (21.62%)	16 / 75 (21.33%)	
occurrences (all)	18	17	
Escherichia urinary tract infection			
subjects affected / exposed	5 / 74 (6.76%)	6 / 75 (8.00%)	
occurrences (all)	5	9	
Nasopharyngitis			
subjects affected / exposed	8 / 74 (10.81%)	8 / 75 (10.67%)	
occurrences (all)	10	10	
Upper respiratory tract infection			
subjects affected / exposed	7 / 74 (9.46%)	8 / 75 (10.67%)	
occurrences (all)	7	9	
Urinary tract infection			
subjects affected / exposed	4 / 74 (5.41%)	10 / 75 (13.33%)	
occurrences (all)	5	17	
Urinary tract infection bacterial			
subjects affected / exposed	3 / 74 (4.05%)	8 / 75 (10.67%)	
occurrences (all)	5	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 74 (6.76%)	3 / 75 (4.00%)	
occurrences (all)	5	3	
Hyperlipidaemia			

subjects affected / exposed	3 / 74 (4.05%)	4 / 75 (5.33%)	
occurrences (all)	3	4	
Hyperkalaemia			
subjects affected / exposed	8 / 74 (10.81%)	12 / 75 (16.00%)	
occurrences (all)	8	16	
Hyperglycaemia			
subjects affected / exposed	5 / 74 (6.76%)	2 / 75 (2.67%)	
occurrences (all)	6	2	
Hypercalcaemia			
subjects affected / exposed	5 / 74 (6.76%)	4 / 75 (5.33%)	
occurrences (all)	5	4	
Diabetes mellitus			
subjects affected / exposed	1 / 74 (1.35%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
Hypoglycaemia			
subjects affected / exposed	6 / 74 (8.11%)	1 / 75 (1.33%)	
occurrences (all)	7	1	
Hypomagnesaemia			
subjects affected / exposed	6 / 74 (8.11%)	7 / 75 (9.33%)	
occurrences (all)	6	13	
Hyponatraemia			
subjects affected / exposed	1 / 74 (1.35%)	5 / 75 (6.67%)	
occurrences (all)	1	7	
Hypophosphataemia			
subjects affected / exposed	7 / 74 (9.46%)	7 / 75 (9.33%)	
occurrences (all)	8	8	
Metabolic acidosis			
subjects affected / exposed	4 / 74 (5.41%)	11 / 75 (14.67%)	
occurrences (all)	4	12	
Vitamin D deficiency			
subjects affected / exposed	4 / 74 (5.41%)	7 / 75 (9.33%)	
occurrences (all)	4	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	Key changes in Substantial Amendment 1, dated 13 Aug 2013, are summarized below. • Patients with graft failure would be discontinued from treatment • 1-sided P value (not 2-sided) would be used for testing the hypothesis • Urinalysis with microscopic evaluation was added to the safety labs • Vital signs for reactogenicity assessments were added • Screening laboratory tests could be repeated once • Collect creatinine values during the long-term follow-up period, if available
06 January 2014	Key changes in Substantial Amendment 2, dated 06 Jan 2014, are summarized below. ● Screening period could begin -14 days from transplant to day of randomization ● Redefined CMV viremia as plasma viral load ≥ 1000 IU/mL ● Expanded stratification criteria for ATG to day of randomization ● Revised CMV AVP period of adjustment to after the day of randomization ● Added vital signs and evaluation of patients 15 minutes after study drug injection ● Inclusion Criterion 5 - clarified patients received valganciclovir or ganciclovir per regulatory label (package insert) ● Exclusion Criteria: Excluded patients who required dialysis on day of randomization, Deleted criterion that excluded patients who had an episode of hyperacute or acuterejection prior to Randomization, Excluded patients who received eculizumab, bortezomib, and intravenous immunoglobulin (IVIG) and/or plasmapheresis from day of transplantation through day of randomization, Clarified contraindications to prophylaxis of CMV viremia/disease with valganciclovir and ganciclovir, Clarified a contraindication to an intramuscular injection also included those who were expected to have a contraindication to the injection, Clarified aspartate aminotransferase (AST) or alanine aminotransferase (ALT) criteria was within 3 days prior to randomization, Concomitant medications – included several clarifications (dose adjustments, interruptions to therapy, time periods for prohibited medications, recording) and additional prohibited medications, Spontaneously reported SAEs during long-term follow-up that were possibly or probably related to study drug should be reported. ● Patients with a temperature ≥ 100.4°F should not receive study drug ● Transplant surgery on day 0 would not be considered an AE or SAE

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.

N/A

Notes: