Clinical trial results:
Evaluation of the Benefits and Risks in Maintenance Renal Transplant Recipients Following Conversion to Nulojix® (belatacept)-based Immunosuppression

Summary

EudraCT number	2012-001314-42
Trial protocol	SE AT DE FR
Global end of trial date	14 October 2019

Results information

Result version number	v1 (current)
This version publication date	08 November 2020
First version publication date	08 November 2020

Trial information

Trial identification

Sponsor protocol code	IM103-116

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	06 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate patient and functional graft survival in maintenance renal transplant recipients (6 - 60 months post-transplantation) converted from CNI to belatacept-based immunosuppression as compared to those continuing CNI based immunosuppression at 24 months post-randomization.

Protection of trial subjects:

The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 185
Country: Number of subjects enrolled	Argentina: 64
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 96
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 3
Worldwide total number of subjects	446
EEA total number of subjects	186

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	370
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

631 Subjects Enrolled, 446 randomized and Treated

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Belatacept

Arm description:

Participants who converted to belatacept treatment from CNI-Based

Arm type	Active comparator
Investigational medicinal product name	Belatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use, Intravascular use

Dosage and administration details:

Injection 250 mg / vial

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

will be administered according to the package insert. Daily MMF should be administered in 2 divided doses on a consistent schedule in relation
to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Enteric-coated Mycophenolate sodium/ Mycophenolic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

will be administered according to the package insert. Daily EC-MPS/MPA should be administered in 2 divided doses on a consistent schedule in relation
to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Subjects should be maintained on a stable daily dose of corticosteroids for the duration of the study unless a change in the medical condition of the subject warrants adjustment. Withdrawal of corticosteroids during the study is not permitted.

Arm title	CNI-Based Regimen

Arm description:

Participants who continued on CNI-Based regimens

Arm type	Active comparator
Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

doses should be adjusted to maintain trough serum concentrations in the range of 50 - 250 ng/mL

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

doses should be adjusted to maintain trough serum concentrations in the range of 4 - 11 ng/mL

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

will be administered according to the package insert. Daily MMF should be administered in 2 divided doses on a consistent schedule in relation
to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Enteric-coated Mycophenolate sodium/ Mycophenolic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

will be administered according to the package insert. Daily EC-MPS/MPA should be administered in 2 divided doses on a consistent schedule in relation
to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects should be maintained on a stable daily dose of corticosteroids for the duration of the study unless a change in the medical condition of the subject warrants adjustment. Withdrawal of corticosteroids during the study is not permitted.

Number of subjects in period 1	Belatacept	CNI-Based Regimen
Started	223	223
Completed	221	222
Not completed	2	1
Not Treated	2	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Belatacept

Arm description:

Participants who converted to belatacept treatment from CNI-Based

Arm type	Active comparator
Investigational medicinal product name	Belatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

Injection 250 mg / vial

Investigational medicinal product name	Mycophenolate Mofeti
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

will be administered according to the package insert. Daily MMF should be administered in 2 divided doses on a consistent schedule in relation to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Enteric-coated Mycophenolate sodium/ Mycophenolic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

will be administered according to the package insert. Daily EC-MPS/MPA should be administered in 2 divided doses on a consistent schedule in relation to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The

dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects should be maintained on a stable daily dose of corticosteroids for the duration of the study unless a change in the medical condition of the subject warrants adjustment. Withdrawal of corticosteroids during the study is not permitted.

Arm title	CNI-Based Regimen

Arm description:

Participants who continued on CNI-Based regimens

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

doses should be adjusted to maintain trough serum concentrations in the range of 4 - 11 ng/mL

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

doses should be adjusted to maintain trough serum concentrations in the range of 50 - 250 ng/mL

Investigational medicinal product name	Mycophenolate Mofeti
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

will be administered according to the package insert. Daily MMF should be administered in 2 divided doses on a consistent schedule in relation to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Enteric-coated Mycophenolate sodium/ Mycophenolic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

will be administered according to the package insert. Daily EC-MPS/MPA should be administered in 2 divided doses on a consistent schedule in relation to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator’s discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects should be maintained on a stable daily dose of corticosteroids for the duration of the study unless a change in the medical condition of the subject warrants adjustment. Withdrawal of corticosteroids during the study is not permitted.

Number of subjects in period 2	Belatacept	CNI-Based Regimen
Started	221	222
Completed	195	186
Not completed	26	36
Adverse event, serious fatal	3	3
withdrew consent	1	2
request to discontinue	6	11
Adverse event, non-fatal	12	7
No longer meets study criteria	3	10
poor/non compliance	-	3
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Belatacept
Reporting group description:	
Participants who converted to belatacept treatment from CNI-Based	
Reporting group title	CNI-Based Regimen
Reporting group description:	
Participants who continued on CNI-Based regimens	

Reporting group values	Belatacept	CNI-Based Regimen	Total
Number of subjects	223	223	446
Age categorical Units: Subjects			
Adults (18-64 years)	184	186	370
From 65-84 years	39	37	76
Age Continuous Units: Years			
median	55.0	54.0	
standard deviation	± 11.3	± 11.7	-
Sex: Female, Male Units: Participants			
Female	73	72	145
Male	150	151	301
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	3	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	24	24	48
White	191	187	378
More than one race	0	0	0
Unknown or Not Reported	7	9	16
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	15	24
Not Hispanic or Latino	82	79	161
Unknown or Not Reported	132	129	261

End points

End points reporting groups	
Reporting group title	Belatacept
Reporting group description: Participants who converted to belatacept treatment from CNI-Based	
Reporting group title	CNI-Based Regimen
Reporting group description: Participants who continued on CNI-Based regimens	
Reporting group title	Belatacept
Reporting group description: Participants who converted to belatacept treatment from CNI-Based	
Reporting group title	CNI-Based Regimen
Reporting group description: Participants who continued on CNI-Based regimens	

Primary: Percentage of participants who survive with a functional graft at 24 months	
End point title	Percentage of participants who survive with a functional graft at 24 months
End point description: Percentage of participants who survive with a functional graft at 24 months post-randomization	
End point type	Primary
End point timeframe: at 24 Months	

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Percentage				
number (confidence interval 95%)	98.2 (95.5 to 99.5)	97.3 (95.2 to 99.4)		

Statistical analyses

Statistical analysis title	Difference between belatacept and CNI
Comparison groups	Belatacept v CNI-Based Regimen

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Proportion of Difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	10.4

Secondary: Percentage of participants who survive with a functional graft at 12 months

End point title	Percentage of participants who survive with a functional graft at 12 months
End point description:	
Percentage of participants who survive with a functional graft at 12 months post-randomization	
End point type	Secondary
End point timeframe:	
at 12 Months	

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Percentage				
number (confidence interval 95%)	98.7 (96.1 to 99.7)	99.1 (96.8 to 99.9)		

Statistical analyses

Statistical analysis title	difference between belatacept and CNI
Comparison groups	Belatacept v CNI-Based Regimen
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Proportion of Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	9

Secondary: Number of participants with a Biopsy Proven Acute Rejection (BPAR)

End point title	Number of participants with a Biopsy Proven Acute Rejection (BPAR)

End point description:

The number of clinically suspected, biopsy proven acute rejection (AR) at 12 and 24 months post-randomization

includes subjects with at least one cellular and/or humoral BPAR event.

End point type	Secondary

End point timeframe:

at 12 and 24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Participants				
at 12 Months	18	4		
at 24 Months	18	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with varying severity of BPAR

End point title	Number of Participants with varying severity of BPAR

End point description:

Number of participants in each severity of clinically suspected, biopsy proven acute rejection (AR) at 12 and 24 months post-randomization

End point type	Secondary

End point timeframe:

at 12 and 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: participants				
at 12 Months|Mild Acute (IA)	2	2		
at 24 Months|Mild Acute (IA)	2	4		
at 12 Months|Mild Acute (IB)1	1	0		
at 24 Months|Mild Acute (IB)1	1	0		

at 12 Months|Moderate Acute (IIA)	7	0		
at 24 Months|Moderate Acute (IIA)	7	1		
at 12 Months|Moderate Acute (IIB)	6	0		
at 24 Months|Moderate Acute (IIB)	6	0		
at 12 Months|Severe Acute (III)	4	1		
at 24 Months|Severe Acute (III)	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of Calculated Glomerular Filtration Rate (cGFR) - Percent Change

End point title	Mean change from baseline of Calculated Glomerular Filtration Rate (cGFR) - Percent Change

End point description:

Mean change from baseline cGFR as calculated by the 4-variable MDRD equation to 12 and 24 months post-randomization - Percent Change

End point type	Secondary

End point timeframe:

at 12 and 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mL/min/1.73m²				
arithmetic mean (confidence interval 95%)				
at 12 Months	13.2 (10.4 to 16.0)	-0.3 (-2.9 to 2.4)		
at 24 Months	15.2 (11.9 to 18.6)	0.3 (-2.9 to 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of Calculated Glomerular Filtration Rate (cGFR) - Adjusted Change

End point title	Mean change from baseline of Calculated Glomerular Filtration Rate (cGFR) - Adjusted Change

End point description:

Mean change from baseline cGFR as calculated by the 4-variable MDRD equation to 12 and 24 months post-randomization - Adjusted Change

End point type	Secondary

End point timeframe:
at 12 and 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mL/min/1.73m²				
arithmetic mean (confidence interval 95%)				
at 12 Months	5.6 (4.3 to 6.9)	-0.7 (-2.0 to 0.6)		
at 24 Months	6.2 (4.7 to 7.7)	-1.0 (-2.6 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Calculated Glomerular Filtration Rate (cGFR)

End point title	Mean Calculated Glomerular Filtration Rate (cGFR)

End point description:
Mean cGFR by study visit, as calculated by the 4-variable MDRD equation.

End point type	Secondary

End point timeframe:
up to 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mL/min/1.73m²				
arithmetic mean (confidence interval 95%)				
Screening	49.8 (48.2 to 51.5)	49.7 (48.2 to 51.2)		
Baseline	49.6 (48.0 to 51.2)	50.7 (49.2 to 52.2)		
Month 3	53.0 (51.1 to 54.9)	50.2 (48.3 to 52.0)		
Month 6	53.3 (51.3 to 55.3)	50.9 (49.1 to 52.7)		
Month 9	53.7 (51.8 to 55.6)	50.7 (48.9 to 52.5)		
Month 12	55.5 (53.4 to 57.6)	50.5 (48.7 to 52.4)		
Month 18	56.5 (54.5 to 58.5)	51.3 (49.2 to 53.4)		

Month 24	55.7 (53.7 to 57.7)	51.1 (49.0 to 53.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Slope Analysis of cGFR

End point title	Slope Analysis of cGFR

End point description:

Slopes of cGFR as plotted from baseline as well as from Month 3, to Month 12 and Month 24 post-randomization

End point type	Secondary

End point timeframe:

at 12 and 24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mL/min/1.73m²/month				
number (confidence interval 95%)				
Baseline to 12 Months	0.241 (0.103 to 0.378)	0.004 (-0.137 to 0.145)		
Month 3 to Month 12	0.281 (0.072 to 0.490)	-0.159 (-0.372 to 0.055)		
Baseline to Month 24	0.685 (0.426 to 0.945)	-0.112 (-0.379 to 0.155)		
Month 3 to Month 24	0.658 (0.332 to 0.984)	-0.277 (-0.614 to 0.060)		

Statistical analyses

No statistical analyses for this end point

Secondary: Slope Analysis of 1/Serum Creatinine

End point title	Slope Analysis of 1/Serum Creatinine

End point description:

Slopes of 1/serum creatinine as plotted from baseline as well as from Month 3, to Month 12 and Month 24 post-randomization

End point type	Secondary

End point timeframe:

at 12 and 24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mL/min/1.73m²/month				
number (confidence interval 95%)				
Baseline to 12 Months	0.034 (0.016 to 0.051)	-0.003 (-0.020 to 0.015)		
Month 3 to Month 12	0.033 (0.007 to 0.059)	-0.021 (-0.048 to 0.006)		
Baseline to Month 24	0.00868 (0.00537 to 0.01199)	-0.00203 (-0.00544 to 0.00138)		
Month 3 to Month 24	0.00814 (0.00412 to 0.01217)	-0.00425 (-0.00842 to -0.00009)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with > 5% and >10% improvement over baseline cGFR

End point title	Percentage of participants with > 5% and >10% improvement over baseline cGFR

End point description:

Percentage of participants with > 5% and >10% improvement over baseline cGFR, at 12 and 24 months post-randomization

End point type	Secondary

End point timeframe:

at 12 and 24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Percentage				
number (not applicable)				
>5% improvement at 12 months	53.4	28.7		
>10% improvement at 12 months	43.9	21.5		
>5% improvement at 24 months	54.3	29.6		
>10% improvement at 24 months	48.4	22.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean urine protein/ creatinine ratio (UPCR)

End point title	Mean urine protein/ creatinine ratio (UPCR)

End point description:

Urine protein/ creatinine ratio (UPCR) at baseline, 3, 6, 12 and 24 months post randomization

End point type	Secondary

End point timeframe:

Up to 24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mg/mmol				
arithmetic mean (confidence interval 95%)				
at Baseline	17.80 (16.03 to 19.58)	18.61 (15.08 to 22.14)		
at 3 months	22.87 (19.88 to 25.86)	20.61 (15.50 to 25.73)		
at 6 months	23.42 (19.71 to 27.12)	20.85 (15.36 to 26.35)		
at 12 months	29.11 (21.86 to 36.35)	21.67 (17.70 to 25.65)		
at 24 months	28.81 (23.71 to 33.91)	24.56 (19.01 to 30.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in systolic and diastolic blood pressure

End point title	Mean change from baseline in systolic and diastolic blood pressure

End point description:

Mean change in systolic and diastolic blood pressure from baseline to 12 and 24 months post randomization

End point type	Secondary

End point timeframe:

at 12 and 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mmHg				
arithmetic mean (confidence interval 90%)				
Diastolic BP at 12 Months	-1.5 (-2.9 to 0.0)	-0.6 (-2.1 to 1.0)		
Diastolic BP at 24 Months	-1.7 (-3.3 to 0.0)	0.5 (-1.3 to 2.3)		
Systolic BP at 12 Months	-1.6 (-4.0 to 0.9)	0.1 (-2.5 to 2.8)		
Systolic BP at 24 Months	-1.3 (-4.1 to 1.6)	1.2 (-1.7 to 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of antihypertensive medications used to control hypertension

End point title	Number of antihypertensive medications used to control hypertension

End point description:

The total number of antihypertensive medications used to control hypertension

End point type	Secondary

End point timeframe:

at baseline, 12 and 24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Number of medications				
arithmetic mean (full range (min-max))				
at Baseline	2.1 (1 to 5)	2.2 (1 to 6)		
at 12 Months	2.3 (1 to 7)	2.2 (1 to 6)		
at 24 Mnths	2.3 (1 to 8)	2.3 (1 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with donor specific antibodies (DSA)

End point title	Number of participants with donor specific antibodies (DSA)

End point description:

Number of participants with donor specific antibodies (DSA) at Baseline/Day 1, and Months 12 and 24 post-randomization

End point type	Secondary

End point timeframe:

at baseline, 12 and 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Participants				
Pre existing at baseline	10	26		
De Novo at 12 Months	2	9		
De Novo at 24 Months	2	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of symptom occurrence and Symptom Distress

End point title	Mean number of symptom occurrence and Symptom Distress

End point description:

The frequency of symptom occurrence and symptom distress as measured with the Modified Transplant Symptom Occurrence and Symptom Distress Scale-59R (MTSOSD-59R) at baseline, Week 6, and Months 3, 6, and 12 post-randomization. Higher scores in the MTSOSD-59R indicate a greater symptom and symptom distress burden than lower scores.

End point type	Secondary

End point timeframe:

up to 12 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	222		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline symptom occurrence	87.8 (± 20.06)	90.7 (± 21.04)		
Baseline symptom distress	28.7 (± 27.07)	34.8 (± 28.30)		
week 6 symptom occurrence	79.0 (± 16.52)	88.6 (± 21.36)		
week 6 symptom distress	19.8 (± 21.41)	32.4 (± 29.55)		
Month 3 symptom occurrence	80.5 (± 16.74)	89.9 (± 23.45)		
Month 3 symptom distress	21.4 (± 23.08)	35.2 (± 32.04)		
month 6 symptom occurrence	80.5 (± 17.50)	91.8 (± 23.72)		
month 6 symptom distress	22.4 (± 22.18)	36.3 (± 31.39)		

month 12 symptom occurrence	82.3 (± 20.08)	91.0 (± 22.33)		
month 12 symptom distress	25.8 (± 25.32)	34.4 (± 30.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an adverse event of special interest

End point title	Number of participants with an adverse event of special interest

End point description:

Number of participants with an adverse event of special interests. Adverse events of special interest include: Serious Infections, Post-Transplant Lymphoproliferative Disorder (PTLD), Progressive multifocal leukoencephalopathy (PML), Malignancies (other than PTLD) including non-melanoma skin carcinomas, Tuberculosis Infections, CNS infections, Viral Infections and Infusion related reactions.

End point type	Secondary

End point timeframe:

24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	222		
Units: participants				
Serious Infections	37	44		
PTLD	1	0		
PML	0	0		
Malignancies	17	12		
Tuberculosis infections	0	0		
CNS Infections	0	0		
Viral Infections	5	9		
Infusion Related Reactions	13	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Marked Laboratory Abnormalities

End point title	Number of participants with Marked Laboratory Abnormalities

End point description:

Number of participants with Marked Laboratory Abnormalities

End point type	Secondary

End point timeframe:

24 Months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	222		
Units: Participants				
Hemoglobin (Abnormal Low)	0	0		
Hemoglobin (Abnormal high)	0	0		
Platelet count (Abnormal low)	0	1		
Leukocytes (Abnormal low)	0	0		
Lymphocytes (Abnormal low)	29	10		
Lymphocytes (Abnormal high)	0	0		
Neutrophils Absolute (Abnormal low)	5	3		
Alanine Aminotransferase (Abnormal High)	0	0		
Alkaline Phosphatase (Abnormal High)	0	0		
Aspartate Aminotransferase (Abnormal High)	0	1		
Total Bilirubin (Abnormal High)	0	0		
Creatine (Abnormal High)	5	4		
Protein/Creatinine Ratio (Abnormal High)	0	0		
Bicarbonate (Abnormal High)	0	1		
Total Calcium (Abnormal low)	0	3		
Total Calcium (Abnormal high)	1	2		
Magnesium (Abnormal low)	0	0		
Magnesium (Abnormal high)	0	0		
Phosphorus (Abnormal Low)	14	12		
Potassium (Abnormal low)	3	2		
Potassium (Abnormal high)	1	5		
Sodium (Abnormal low)	4	9		
Sodium (Abnormal high)	0	1		
Albumin (Abnormal low)	0	0		
Total Cholesterol (Abnormal High)	13	17		
Serum Glucose (Abnormal low)	0	0		
Serum Glucose (Abnormal high)	18	18		
Triglycerides (Abnormal high)	2	2		
Uric Acid (Abnormal high)	15	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in vital signs: Heart Rate

End point title	Mean change from baseline in vital signs: Heart Rate

End point description:

The mean change from baseline in measured heart rate

End point type	Secondary

End point timeframe:
at 12 and 24 months

End point values	Belatacept	CNI-Based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	222		
Units: beats per minute (bpm)				
arithmetic mean (confidence interval 95%)				
Change from baseline at 12 months	-1.8 (-3.3 to -0.2)	-0.6 (-2.2 to 1.0)		
Change from baseline at 24 months	-1.9 (-3.5 to -0.3)	1.0 (-0.8 to 2.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from start of treatment up to 30 days after last treatment dose.	
Adverse event reporting additional description:	
Adverse events were calculated up to 24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	CNI-Based Regimen
Reporting group description:	
Subjects randomized to continued their CNI-based regimen, received doses targeted to achieve trough serum concentrations (C0 levels) of 50 - 250 nanograms per milliliter (ng/mL) Cyclosporine (CsA) or 4 - 11 ng/mL Tacrolimus (TAC).	
Reporting group title	Belatacept
Reporting group description:	
Subjects received an infusion of belatacept, 5 milligrams per kilogram (mg/kg) intravenously (IV) on Days 1, 15, 29, 43, 57, and every 28 days thereafter. Each dose was based on the Day 1 body weight (baseline weight), and was not to be modified unless body weight increased or decreased by more than or equal to 10% from Day 1. The infusion solution was administered over a period of approximately 30 minutes. The Calcineurin Inhibitors (CNI) dose was tapered to 40% - 60% of the baseline dose by Day 15, 20% - 30% of the baseline dose by Day 22, and was then discontinued by Day 29 (± 3 days).	

Serious adverse events	CNI-Based Regimen	Belatacept	
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 222 (43.69%)	108 / 221 (48.87%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	5 / 222 (2.25%)	11 / 221 (4.98%)	
occurrences causally related to treatment / all	4 / 6	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post transplant lymphoproliferative disorder			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer recurrent			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	5 / 222 (2.25%)	3 / 221 (1.36%)	
occurrences causally related to treatment / all	3 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 222 (0.45%)	4 / 221 (1.81%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 222 (0.45%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 222 (0.90%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			

Chronic allograft nephropathy			
subjects affected / exposed	2 / 222 (0.90%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	8 / 222 (3.60%)	19 / 221 (8.60%)	
occurrences causally related to treatment / all	1 / 9	13 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterovaginal prolapse			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvar dysplasia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 222 (0.90%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus polyp			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive delusion			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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	2 / 222 (0.90%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Donor specific antibody present			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus test positive			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
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			
Accidental overdose			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical vertebral fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	2 / 222 (0.90%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 13	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt blood flow excessive			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt occlusion			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft loss			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	0 / 222 (0.00%)	3 / 221 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 222 (0.45%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
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	1 / 222 (0.45%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 222 (1.35%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 222 (0.45%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 222 (0.90%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery stenosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 222 (1.35%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monocytosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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 hernia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 222 (2.70%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	2 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 222 (0.90%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 222 (2.25%)	4 / 221 (1.81%)	
occurrences causally related to treatment / all	1 / 7	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder diverticulum			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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			
Back pain			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematoma muscle			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 222 (0.90%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 222 (0.00%)	3 / 221 (1.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 222 (1.35%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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 / 222 (0.90%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
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	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	6 / 222 (2.70%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	0 / 222 (0.00%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis disseminated			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infected cyst			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 222 (0.90%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising soft tissue infection			

subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 222 (0.45%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 222 (3.15%)	5 / 221 (2.26%)	
occurrences causally related to treatment / all	0 / 7	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	2 / 222 (0.90%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal graft infection			
subjects affected / exposed	1 / 222 (0.45%)	2 / 221 (0.90%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 222 (0.90%)	4 / 221 (1.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	8 / 222 (3.60%)	7 / 221 (3.17%)	
occurrences causally related to treatment / all	1 / 17	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	3 / 222 (1.35%)	6 / 221 (2.71%)	
occurrences causally related to treatment / all	1 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 222 (0.90%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bk virus infection			
subjects affected / exposed	2 / 222 (0.90%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 222 (0.45%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	3 / 222 (1.35%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 221 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			

subjects affected / exposed	1 / 222 (0.45%)	0 / 221 (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	CNI-Based Regimen	Belatacept	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 222 (75.23%)	174 / 221 (78.73%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	17 / 222 (7.66%)	20 / 221 (9.05%)	
occurrences (all)	20	23	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 222 (9.46%)	29 / 221 (13.12%)	
occurrences (all)	24	32	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 222 (3.60%)	15 / 221 (6.79%)	
occurrences (all)	9	18	
Headache			
subjects affected / exposed	23 / 222 (10.36%)	27 / 221 (12.22%)	
occurrences (all)	29	35	
Tremor			
subjects affected / exposed	12 / 222 (5.41%)	6 / 221 (2.71%)	
occurrences (all)	13	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 222 (6.76%)	23 / 221 (10.41%)	
occurrences (all)	16	30	
Oedema peripheral			
subjects affected / exposed	35 / 222 (15.77%)	22 / 221 (9.95%)	
occurrences (all)	40	26	
Pyrexia			

subjects affected / exposed	17 / 222 (7.66%)	20 / 221 (9.05%)	
occurrences (all)	18	31	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 222 (5.86%)	12 / 221 (5.43%)	
occurrences (all)	13	12	
Diarrhoea			
subjects affected / exposed	61 / 222 (27.48%)	47 / 221 (21.27%)	
occurrences (all)	77	63	
Nausea			
subjects affected / exposed	11 / 222 (4.95%)	15 / 221 (6.79%)	
occurrences (all)	11	15	
Vomiting			
subjects affected / exposed	13 / 222 (5.86%)	10 / 221 (4.52%)	
occurrences (all)	17	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 222 (9.46%)	31 / 221 (14.03%)	
occurrences (all)	23	41	
Oropharyngeal pain			
subjects affected / exposed	12 / 222 (5.41%)	10 / 221 (4.52%)	
occurrences (all)	15	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 222 (5.41%)	9 / 221 (4.07%)	
occurrences (all)	12	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 222 (10.36%)	21 / 221 (9.50%)	
occurrences (all)	27	25	
Back pain			
subjects affected / exposed	22 / 222 (9.91%)	18 / 221 (8.14%)	
occurrences (all)	24	19	
Musculoskeletal pain			
subjects affected / exposed	12 / 222 (5.41%)	5 / 221 (2.26%)	
occurrences (all)	14	5	

Pain in extremity			
subjects affected / exposed	20 / 222 (9.01%)	11 / 221 (4.98%)	
occurrences (all)	21	11	
Infections and infestations			
Bronchitis			
subjects affected / exposed	18 / 222 (8.11%)	23 / 221 (10.41%)	
occurrences (all)	19	32	
Nasopharyngitis			
subjects affected / exposed	50 / 222 (22.52%)	44 / 221 (19.91%)	
occurrences (all)	75	78	
Upper respiratory tract infection			
subjects affected / exposed	19 / 222 (8.56%)	18 / 221 (8.14%)	
occurrences (all)	29	22	
Urinary tract infection			
subjects affected / exposed	32 / 222 (14.41%)	38 / 221 (17.19%)	
occurrences (all)	75	72	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2013	Modification to the inclusion/exclusion criteria. Clarifications to the time and Events, and Pharmacokinetic Assessments Tables. Inclusion of Clinical criteria for suspicion of PTLD and procedures for monitoring. Update to list of Abbreviations. Minor edits and clarifications throughout the protocol, including table numbering.
04 September 2013	Modification to the inclusion/exclusion criteria. Clarification to the Time and Events and Pharmacokinetic Assessments Tables. Modification to the Renal Biopsy Requirements. Clarification of Live Vaccines for subjects. Addition of re-testing for screening creatinine labs. Minor edits and clarifications throughout the protocol, including table numbering.
20 August 2014	Modification to the inclusion/exclusion criteria. Modification to the MDRD formula, the definition of stable renal function and stable immunosuppression regimen. Addition of re-screening subjects. Extension of screening period. Decrease the frequency of body weight measurements. Minor edits and clarifications throughout the protocol.
07 April 2017	Modification to decrease target enrollment from 600 to 440 randomized subjects. The clarification of wording for the following: the CSPAR endpoint for consistency throughout the protocol; the requirement for daily dosing of maintenance corticosteroids throughout study participation; to indicate that protocol-specified tacrolimus trough levels being locally determined for patient management will also be captured in the clinical database; the timing for determination of post-belatacept infusion vital signs. Limitation of study participation by patients enrolled while receiving maintenance immunosuppression with tacrolimus plus mycophenolate sodium to approximately one-third (1/3) of all subjects. Provide a proviso to allow rescreening of patients who were screen failure earlier in the study. Update the definition of menopause; Correction of typographical errors and minor edits grammatical inconsistencies throughout the protocol.
30 May 2017	To correct two typographical errors on the last revised protocol version 04.
18 April 2018	Update definition of serious breach per company guidelines, clarify belatacept dosing instructions for skipping of doses to include possibility of dosing out of defined visit windows, addition of PML for some biomarker labs, Clarification of "end of infusion" definition, allow provision of central lab CNI trough values to sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported