Clinical trial results:
A phase 2 multi-center, randomized conversion study to evaluate the pharmacokinetics, efficacy, and safety of Belatacept administered to pediatric subjects with a stable renal transplant

Summary

EudraCT number	2011-005257-31
Trial protocol	Outside EU/EEA DE
Global end of trial date	06 December 2016

Results information

Result version number	v1 (current)
This version publication date	16 June 2017
First version publication date	16 June 2017

Trial information

Trial identification

Sponsor protocol code	IM103-144

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01791491
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee 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	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000157-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the pharmacokinetics (PK) efficacy and safety of belatacept in stable pediatric renal transplant recipients.

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	28 October 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: 16
Worldwide total number of subjects	16
EEA total number of subjects	0

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)	16
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 5 sites in the United States.

Pre-assignment

Screening details:

A total of 16 subjects were enrolled and 9 subjects were treated in the study. Reasons for non-treatment: 1 subject withdrew consent and 6 subjects no longer met study criteria.

Period 1

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

Arms

Arm title	Belatacept

Arm description:

A single dose of 7.5 mg/kg Belatacept was given intravenously on study Day 1 over approximately 30 minutes.

Arm type	Experimental
Investigational medicinal product name	Belatacept
Investigational medicinal product code	BMS-224818
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Belatacept (250 mg/vial) was administered to subjects as a single dose intravenous (IV) belatacept 7.5 mg/kg on Study Day 1 over approximately 30 minutes. Appeared as white to off white, whole or fragmented cake in a vial.

Number of subjects in period 1[1]	Belatacept
Started	9
Completed	9

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 16 subjects who were enrolled, only 9 subjects were treated.

Baseline characteristics

Reporting groups	
Reporting group title	Belatacept
Reporting group description:	
A single dose of 7.5 mg/kg Belatacept was given intravenously on study Day 1 over approximately 30 minutes.	

Reporting group values	Belatacept	Total	
Number of subjects	9	9	
Age Categorical Units: Subjects			
Adolescents (12-17 years)	9	9	
Age Continuous Units: years			
arithmetic mean	15.1		
standard deviation	± 1.17	-	
Gender Categorical Units: Subjects			
Female	4	4	
Male	5	5	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	4	4	
White	5	5	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	5	5	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Belatacept

Reporting group description:

A single dose of 7.5 mg/kg Belatacept was given intravenously on study Day 1 over approximately 30 minutes.

Primary: Maximum observed serum concentration (Cmax) of Belatacept

End point title	Maximum observed serum concentration (Cmax) of

End point description:

Cmax was derived from serum concentration versus time data. Serum samples were analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA) and were obtained at: pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57. The results were summarized. The lower limit of assay quantitation (LLOQ) was set to "zero" which was 0.003 micrograms per milliliter (ug/mL). Cmax was measured in micrograms per milliliter. Pharmacokinetic (PK) analysis set: all subjects who received one dose of belatacept and who had at least 1 blood samples drawn for PK determination.

End point type	Primary

End point timeframe:

Pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: micrograms per milliliter				
geometric mean (geometric coefficient of variation)	151 (± 20)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of Maximum Observed Plasma Concentration (Tmax) of Belatacept

End point title	Time of Maximum Observed Plasma Concentration (Tmax) of Belatacept[2]

End point description:

Tmax was derived from serum concentration versus time data. Serum samples were analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA) and were obtained at: pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57. The results were summarized. The lower limit of assay quantitation (LLOQ) was set to "zero" which was 0.003 micrograms per milliliter (ug/mL). Tmax was measured in hours (h). Pharmacokinetic (PK) analysis set: all subjects who received one dose of belatacept and who had at least 1 blood samples drawn for PK determination.

End point type	Primary

End point timeframe:

Pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hours				
median (full range (min-max))	0.733 (0.45 to 2.05)			

Statistical analyses

No statistical analyses for this end point

Primary: Half-Life of Elimination (T-Half) of Belatacept

End point title	Half-Life of Elimination (T-Half) of Belatacept[3]

End point description:

T-HALF was derived from serum concentration versus time data. Serum samples were analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA) and were obtained at: pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57. The results were summarized. The lower limit of assay quantitation (LLOQ) was set to "zero" which was 0.003 micrograms per milliliter (ug/mL). T-HALF was measured in hours (h). Pharmacokinetic (PK) analysis set: all subjects who received one dose of belatacept and who had at least 1 blood samples drawn for PK determination.

End point type	Primary

End point timeframe:

Pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hours				
arithmetic mean (standard deviation)	173 (± 46.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC (0-T)) and Area under the serum concentration-time curve from time zero extrapolated to infinite time (AUC (INF))

of Belatacept

End point title	Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC (0-T)) and Area under the serum concentration-time curve from time zero extrapolated to infinite time (AUC (INF)) of Belatacept[4]

End point description:

AUC (0 - T) and AUC (0 - INF) were derived from serum concentration versus time data and measured in microgram hours per milliliter (µg*h/mL). Serum samples were analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA) and were obtained at: pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57. The results were summarized. The lower limit of assay quantitation (LLOQ) was set to "zero" which was 0.003 micrograms per milliliter (ug/mL). Pharmacokinetic (PK) analysis set: all subjects who received one dose of belatacept and who had at least 1 blood samples drawn for PK determination.

End point type	Primary

End point timeframe:

Pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: microgram hours per milliliter				
geometric mean (geometric coefficient of variation)				
AUC (0-T)	15145 (± 25)			
AUC(INF)	15407 (± 25)			

Statistical analyses

No statistical analyses for this end point

Primary: Total body clearance (CLT) of Belatacept

End point title	Total body clearance (CLT) of Belatacept[5]

End point description:

CLT was the volume of abatacept cleared by the system, normalized by baseline body weight. Serum samples were analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA) and were obtained at: pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57. The results were summarized. The lower limit of assay quantitation (LLOQ) was set to "zero" which was 0.003 micrograms per milliliter (ug/mL). CLT was measured in milliliters per hours per kilogram of body weight (mL/h/kg). Pharmacokinetic (PK) analysis set: all subjects who received one dose of belatacept and who had at least 1 blood samples drawn for PK determination.

End point type	Primary

End point timeframe:

Pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: milliliters per hours per kilogram				
geometric mean (geometric coefficient of variation)	0.483 (± 27)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of distribution at steady-state (Vss) of Belatacept

End point title	Volume of distribution at steady-state (Vss) of Belatacept[6]

End point description:

Vss was derived from serum concentration versus time data. Serum samples were analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA) and were obtained at: pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57. The results were summarized. The lower limit of assay quantitation (LLOQ) was set to "zero" which was 0.003 micrograms per milliliter (ug/mL). Vss was measured in liters per kg body weight (L/kg). Pharmacokinetic (PK) analysis set: all subjects who received one dose of belatacept and who had at least 1 blood samples drawn for PK determination.

End point type	Primary

End point timeframe:

Pre-dose (0 hours), 0.5 and 2 hours from Start of Infusion on Day 1, Day 29, and Day 57

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Liters per kilogram				
geometric mean (geometric coefficient of variation)	0.088 (± 30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Death, Serious adverse events (SAEs), and Treatment-related adverse event (AE)

End point title	Number of Subjects with Death, Serious adverse events (SAEs), and Treatment-related adverse event (AE)

End point description:

Death was a fatal event leading to permanent cessations of all vital functions of the body. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Adverse event (AE) defined: any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal

relationship with treatment. Treatment related=having certain, probable, possible, or missing relationship to study drug. All treated subjects who received at least one dose of belatacept.

End point type	Secondary

End point timeframe:

Date of First Dose to 24 weeks post the last dose; approximately 26 weeks

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: subjects				
Death	0			
SAEs	4			
Treatment-related AEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of CD86 Receptor Occupancy

End point title	Percentage of CD86 Receptor Occupancy

End point description:

Blood samples collected following the single dose belatacept infusion were assessed for the number of occupied CD86 receptors (CD86 RO). Pharmacodynamic analysis set: all subjects who received one dose of belatacept and who had at least 1 pharmacodynamic result (CD86 RO) reported after that dose.

End point type	Secondary

End point timeframe:

0.5 hours post dose on Day 1, Day 29 and Day 57

End point values	Belatacept			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (standard deviation)				
0.5 Hour (n=7)	94.7 (± 4.035)			
Day 29 (n=7)	77.99 (± 10.983)			
Day 57 (n=5)	51.45 (± 43.285)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Belatacept-induced Immunogenicity Response

End point title	Number of Subjects with Positive Belatacept-induced Immunogenicity Response

End point description:

Serum samples were analyzed for anti-belatacept antibodies using a validated homogenous bridging assay. The assay followed a tiered approach consistent with health authority guidance: tier 1 for screening ADA responses, tier 2 for confirming drug specificity of the ADA-positive responses, and tier 3 for titer. A neutralizing antibody assay was used to test those samples positive to the LEA29Y portion of the molecule in tier 2 and for which drug concentrations are =>1 µg/mL. Lack of immunogenicity was defined as the absence of a positive response. All treated subjects who received at least one dose of belatacept.

End point type	Secondary

End point timeframe:

Baseline/Day 1, Days 15, 29, and 57

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were reported from the date of first dose to 24 weeks post the last dose (approximately 26 weeks); AEs were reported for the on study period from the date of first dose up to 56 days post last dose (approximately 10 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Belatacept

Reporting group description:

Subjects received single infusion of belatacept, 7.5 mg/kg, intravenously on study Day 1 over approximately 30 minutes.

Serious adverse events	Belatacept		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Belatacept		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2014	Modification to the inclusion/exclusion criteria. Clarification to the Time and Events and Pharmacokinets Assessment Tables. Minor edits and clarification throughout the protocol, including table numbering.
28 August 2015	Modification to study design- multi dose phase and long term extension removed, modified age range in a pediatric population, decreased in total enrollment, minor edits and clarifications throughout protocol.
13 October 2015	Clarification of PTLD frequencies to be consistent with ICF and to further define end of study visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported