



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) | EMA-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 ($\mu\text{g}\cdot\text{h}/\text{mL}$). 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 ($\mu\text{g}/\text{mL}$). 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 (\pm 25) | | | |
| AUC(INF) | 15407 (\pm 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 ($\mu\text{g}/\text{mL}$). CLT was measured in milliliters per hours per kilogram of body weight ($\text{mL}/\text{h}/\text{kg}$). 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 (\pm 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 (\pm 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: 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 $\mu\text{g/mL}$. 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

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

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 Pharmacokinetics 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