



## Clinical trial results:

### A Phase 3 Multi-center, Open-Label Study to Evaluate Pharmacokinetics, Efficacy and Safety of Abatacept Administered Subcutaneously (SC) in Children and Adolescents with Active Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Inadequate Response (IR) to biologic or non biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2012-003195-39                |
| Trial protocol           | DE BE ES IT Outside EU/EEA FR |
| Global end of trial date |                               |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 12 July 2019 |
| First version publication date | 12 July 2019 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | IM101-301 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01844518 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bristol-Myers Squibb   |
| Sponsor organisation address | Route 206 and Province Line Road, Princeton, United States, NJ 08540-4000            |
| Public contact               | Study Director - Bristol-Myers Squibb, Bristol-Myers Squibb, Clinical.Trials@bms.com |
| Scientific contact           | Study Director - Bristol-Myers Squibb, Bristol-Myers Squibb, 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-000118-PIP02-10 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Interim         |
| Date of interim/final analysis                       | 02 October 2018 |
| Is this the analysis of the primary completion data? | No              |

|                              |    |
|------------------------------|----|
| Global end of trial reached? | No |
|------------------------------|----|

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study is to estimate abatacept steady-state trough serum concentrations (C<sub>min</sub>) at Day 113 in children and adolescents with Polyarticular Juvenile Idiopathic Arthritis (pJIA) aged 6 through 17 years.

Protection of trial subjects:

The study was 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                          | 30 August 2013 |
| Long term follow-up planned                               | Yes            |
| Long term follow-up rationale                             | Safety         |
| Long term follow-up duration                              | 5 Years        |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Belgium: 12           |
| Country: Number of subjects enrolled | Brazil: 6             |
| Country: Number of subjects enrolled | France: 10            |
| Country: Number of subjects enrolled | Germany: 73           |
| Country: Number of subjects enrolled | Italy: 6              |
| Country: Number of subjects enrolled | Mexico: 25            |
| Country: Number of subjects enrolled | Peru: 10              |
| Country: Number of subjects enrolled | Russian Federation: 5 |
| Country: Number of subjects enrolled | Spain: 16             |
| Country: Number of subjects enrolled | South Africa: 19      |
| Country: Number of subjects enrolled | United States: 26     |
| Country: Number of subjects enrolled | Argentina: 26         |
| Worldwide total number of subjects   | 234                   |
| EEA total number of subjects         | 117                   |

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)                     | 128 |
| Adolescents (12-17 years)                 | 106 |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Total 234 participants were enrolled, 220 randomized as 14 participants were screen failures. 219 participants were treated as one participant discontinued prior to being dosed, hence not included in analysis.

### Period 1

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

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | SC Abatacept Ages 6 to 17 |

Arm description:

Subcutaneous (SC) abatacept administered by prefilled syringe (PFS) once weekly according to the following weight-tiered dosing regimen: 10 to less than (<) 25 kilogram (kg) (50 milligram [mg] in 0.4 milliliter [mL] PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Abatacept                                    |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Abatacept was administered once weekly according to the following weight-tiered dosing regimen: 10 to < 25 kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | SC Abatacept Ages 2 to 5 |
|------------------|--------------------------|

Arm description:

All weight-tiered dosing groups receiving SC abatacept administered by prefilled syringe (PFS) once weekly according to weight-tiered dose regimen as follows: 10 to < 25kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Abatacept                                    |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Abatacept was administered once weekly according to the following weight-tiered dosing regimen: 10 to < 25 kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

| Number of subjects in period 1 <sup>[1]</sup> | SC Abatacept Ages 6 to 17 | SC Abatacept Ages 2 to 5 |
|---|---------------------------|--------------------------|
|   |                           |                          |
| Started                                       | 173                       | 46                       |
| Completed                                     | 132                       | 39                       |
| Not completed                                 | 41                        | 7                        |
| Withdrawal of Consent                         | 9                         | -                        |
| Poor/Non-Compliance                           | 1                         | -                        |
| Participant requested to discontinue          | 4                         | 1                        |
| Adverse event, non-fatal                      | 7                         | 1                        |
| No Longer Met Study Criteria                  | 2                         | -                        |
| Pregnancy                                     | 1                         | -                        |
| Lack of efficacy                              | 17                        | 5                        |

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: A total of 234 participants were enrolled, of whom 220 were randomized as 14 participants were screen failures. Of these, 219 participants were treated as one participant discontinued prior to being dosed and was not included in analysis.

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | SC Abatacept Ages 6 to 17 |
|-----------------------|---------------------------|

Reporting group description:

Subcutaneous (SC) abatacept administered by prefilled syringe (PFS) once weekly according to the following weight-tiered dosing regimen: 10 to less than (<) 25 kilogram (kg) (50 milligram [mg] in 0.4 milliliter [mL] PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | SC Abatacept Ages 2 to 5 |
|-----------------------|--------------------------|

Reporting group description:

All weight-tiered dosing groups receiving SC abatacept administered by prefilled syringe (PFS) once weekly according to weight-tiered dose regimen as follows: 10 to < 25kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

| Reporting group values                                | SC Abatacept Ages 6 to 17 | SC Abatacept Ages 2 to 5 | Total |
|---|---------------------------|--------------------------|-------|
| Number of subjects                                    | 173                       | 46                       | 219   |
| Age categorical<br>Units: Subjects                    |                           |                          |       |
| In utero  | 0                         | 0                        | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                         | 0                        | 0     |
| Newborns (0-27 days)                                  | 0                         | 0                        | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                         | 0                        | 0     |
| Children (2-11 years)                                 | 74                        | 46                       | 120   |
| Adolescents (12-17 years)                             | 99                        | 0                        | 99    |
| Adults (18-64 years)                                  | 0                         | 0                        | 0     |
| From 65-84 years                                      | 0                         | 0                        | 0     |
| 85 years and over                                     | 0                         | 0                        | 0     |
| Gender, Male/Female<br>Units: Subjects                |                           |                          |       |
| Female  | 136                       | 28                       | 164   |
| Male  | 37                        | 18                       | 55    |
| Race (NIH/OMB)<br>Units: Subjects                     |                           |                          |       |
| Black or African American                             | 14                        | 1                        | 15    |
| White   | 144                       | 44                       | 188   |
| Other   | 15                        | 1                        | 16    |

## End points

### End points reporting groups

|   |                           |
|---|---------------------------|
| Reporting group title   | SC Abatacept Ages 6 to 17 |
| Reporting group description:<br>Subcutaneous (SC) abatacept administered by prefilled syringe (PFS) once weekly according to the following weight-tiered dosing regimen: 10 to less than (<) 25 kilogram (kg) (50 milligram [mg] in 0.4 milliliter [mL] PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS). |                           |
| Reporting group title   | SC Abatacept Ages 2 to 5  |
| Reporting group description:<br>All weight-tiered dosing groups receiving SC abatacept administered by prefilled syringe (PFS) once weekly according to weight-tiered dose regimen as follows: 10 to < 25kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).                            |                           |
| Subject analysis set title  | 10 to <25 kg Dosing Group |
| Subject analysis set type   | Sub-group analysis        |
| Subject analysis set description:<br>Weight-tiered dosing group received 50 mg SC abatacept administered to 6 to 17 year old participants by PFS once weekly.   |                           |
| Subject analysis set title  | 25 to <50 kg Dosing Group |
| Subject analysis set type   | Sub-group analysis        |
| Subject analysis set description:<br>Weight-tiered dosing group received 87.5 mg SC abatacept administered to 6 to 17 year old participants by PFS once weekly.   |                           |
| Subject analysis set title  | >=50 kg Dosing Group      |
| Subject analysis set type   | Sub-group analysis        |
| Subject analysis set description:<br>Weight-tiered dosing group received 125 mg SC abatacept administered to 6 to 17 year old participants by PFS once weekly.  |                           |

### Primary: Abatacept Trough Concentration (Cmin) in Subjects Ages 6 to 17

|  |  |
|--|--|
| End point title  | Abatacept Trough Concentration (Cmin) in Subjects Ages 6 to 17 <sup>[1][2]</sup> |
| End point description:<br>Trough concentration of abatacept (reported as geometric mean of Cmin) in all pharmacokinetic (PK)-evaluable subjects. Cmin is reported in microgram per milliliter (µg/mL). Desired target therapeutic Cmin should be ≥ 10 µg/mL. Evaluable pharmacokinetic (PK) analysis population at Day 113 included all the subjects whose PK measurements were collected in the 4 to 10 day window after the previous SC dose and prior to Day 113 dose and if 7 consecutive weekly SC abatacept injections of the same dose were administered prior to Day 113. Here 'N' 'number of subjects analyzed' signifies subjects who were evaluable for this time point. As per planned analysis results were reported for this arm only. |  |
| End point type   | Primary  |
| End point timeframe:<br>Day 113  |  |

#### 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 summary statistics were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only summary statistics were planned for this endpoint.

|   |                              |  |  |  |
|---|------------------------------|--|--|--|
| <b>End point values</b>                             | SC Abatacept<br>Ages 6 to 17 |  |  |  |
| Subject group type                                  | Reporting group              |  |  |  |
| Number of subjects analysed                         | 131                          |  |  |  |
| Units: µg/mL  |                              |  |  |  |
| geometric mean (geometric coefficient of variation) |                              |  |  |  |
| Cmin  | 39.7 (± 35)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects (ages 6 to 17) Achieving American College of Rheumatology Pediatric 30 Response (ACRp30)

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects (ages 6 to 17) Achieving American College of Rheumatology Pediatric 30 Response (ACRp30) <sup>[3]</sup> |
|-----------------|--|

End point description:

ACRp30 is defined as ≥30% improvement in at least 3 of the 6 juvenile idiopathic arthritis (JIA) core set variables [number of active joints, number of joints with limitation of motion (LOM), physician global assessment of disease activity, parent global assessment of patient overall well-being, functional ability as measured by the Children's Health Assessment Questionnaire (CHAQ) and C-reactive protein (CRP)] and ≥30% worsening in not more than 1 of the remaining 6 JIA core set variables. All treated population included all participants who received at least one dose of study medication.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 113

Notes:

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

Justification: Only summary statistics were planned for this endpoint.

|                                  |                              |  |  |  |
|----------------------------------|------------------------------|--|--|--|
| <b>End point values</b>          | SC Abatacept<br>Ages 6 to 17 |  |  |  |
| Subject group type               | Reporting group              |  |  |  |
| Number of subjects analysed      | 173                          |  |  |  |
| Units: Percentage of subjects    |                              |  |  |  |
| number (confidence interval 95%) |                              |  |  |  |
| ACRp30                           | 80.9 (75.1 to 86.8)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abatacept Trough Concentration (Cmin) in Subjects Ages 6 to 17 by Weight Tier Dose

|                 |  |
|-----------------|--|
| End point title | Abatacept Trough Concentration (Cmin) in Subjects Ages 6 to 17 by Weight Tier Dose |
|-----------------|--|

End point description:

Evaluation of the trough concentration of abatacept (reported as geometric mean of Cmin) in all pk-



evaluable subjects at Days 57, 85 and 113 during a 4-month treatment period. Weight-tiered dosing groups are based on the first dose the subject received. Cmin is reported in microgram per milliliter (µg/mL). Evaluable PK analysis population at Days 57 or 85 included all the subjects whose PK measurements were collected in the 4 to 10 day window after the previous SC dose and prior to the Day 57 dose or Day 85 dose, respectively; and for Day 113 included all the subjects whose PK measurements were collected in the 4 to 10 day window after the previous SC dose and prior to Day 113 dose and if 7 consecutive weekly SC abatacept injections of the same dose were administered prior to Day 113. Here 'n' 'number analyzed' signifies subjects who were evaluable for each time point. As per planned analysis results were reported for this arm only.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Days 57, 85 and 113  |           |

| End point values                                    | 10 to <25 kg<br>Dosing Group | 25 to <50 kg<br>Dosing Group | >=50 kg<br>Dosing Group |  |
|---|------------------------------|------------------------------|-------------------------|--|
| Subject group type                                  | Subject analysis set         | Subject analysis set         | Subject analysis set    |  |
| Number of subjects analysed                         | 18                           | 74                           | 81                      |  |
| Units: µg/mL  |                              |                              |                         |  |
| geometric mean (geometric coefficient of variation) |                              |                              |                         |  |
| Day 57 (n =14, 69, 75)                              | 29.5 (± 32)                  | 36.2 (± 35)                  | 33.3 (± 33)             |  |
| Day 85 (n= 17, 64, 65)                              | 27.7 (± 38)                  | 42.5 (± 32)                  | 36.0 (± 40)             |  |
| Day 113 (n= 14, 62, 59)                             | 34.3 (± 39)                  | 44.2 (± 34)                  | 36.3 (± 31)             |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects (ages 6 to 17) with Adverse Events (AEs), Deaths, Serious AEs (SAEs) and AEs Leading to Discontinuation in the Short Term Period

|                 |  |
|-----------------|--|
| End point title | Number of Subjects (ages 6 to 17) with Adverse Events (AEs), Deaths, Serious AEs (SAEs) and AEs Leading to Discontinuation in the Short Term Period <sup>[4]</sup> |
|-----------------|--|

End point description:

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. A SAE is any untoward medical occurrence that at any dose which results in death, is life threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect. All treated population included all subjects who received at least one dose of study medication. As per planned analysis results were reported for this arm only.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Day 1 up to 56 days post last dose in short-term period or first dose in long-term period whichever is first |           |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only summary statistics were planned for this endpoint.

|                             |                              |  |  |  |
|-----------------------------|------------------------------|--|--|--|
| <b>End point values</b>     | SC Abatacept<br>Ages 6 to 17 |  |  |  |
| Subject group type          | Reporting group              |  |  |  |
| Number of subjects analysed | 173                          |  |  |  |
| Units: Subjects             |                              |  |  |  |
| Deaths                      | 0                            |  |  |  |
| SAEs                        | 5                            |  |  |  |
| Drug-Related SAEs           | 1                            |  |  |  |
| Discontinuation due to SAEs | 2                            |  |  |  |
| Drug-Related AEs            | 36                           |  |  |  |
| Discontinuation due to AEs  | 3                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Adverse Events (AEs), Deaths, Serious AEs and AEs Leading to Discontinuation in the Cumulative Period

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Adverse Events (AEs), Deaths, Serious AEs and AEs Leading to Discontinuation in the Cumulative Period |
|-----------------|---|

End point description:

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. A SAE is any untoward medical occurrence that at any dose which results in death, is life threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect. All treated population included all subjects who received at least one dose of study medication. As per planned analysis results were reported for this arm only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 up to 56 days after last dose ( up to 2 years)

|                             |                              |                             |  |  |
|-----------------------------|------------------------------|-----------------------------|--|--|
| <b>End point values</b>     | SC Abatacept<br>Ages 6 to 17 | SC Abatacept<br>Ages 2 to 5 |  |  |
| Subject group type          | Reporting group              | Reporting group             |  |  |
| Number of subjects analysed | 173                          | 46                          |  |  |
| Units: Subjects             |                              |                             |  |  |
| Deaths                      | 0                            | 0                           |  |  |
| SAEs                        | 14                           | 5                           |  |  |
| Drug-Related SAEs           | 1                            | 2                           |  |  |
| Discontinuation Due to SAEs | 4                            | 0                           |  |  |
| Treatment-Related AEs       | 54                           | 30                          |  |  |
| Discontinuation Due to AEs  | 4                            | 1                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects (ages 6 to 17) with Positive Immunogenicity Response in the Short Term Period

|                 |   |
|-----------------|---|
| End point title | Number of Subjects (ages 6 to 17) with Positive Immunogenicity Response in the Short Term Period <sup>[5]</sup> |
|-----------------|---|

End point description:

Overall number of subjects with either a positive immunogenicity response for 'CTLA4 and possibly Ig' or 'Ig and/or Junction Region' relative to baseline. Sample draws for immunogenicity were scheduled at specific study days while on treatment for all subjects and at follow-up visits 28, 85, and 168 days after the last abatacept dose for those subjects who discontinued from the ST period or completed the ST study without continuing abatacept treatment. Immunogenicity analysis population: who received at least one dose of study medication and who had at least 1 immunogenicity result reported after start of study medication. Here 'N' number of participants analyzed signifies participants who were evaluable for this outcome measure. As per planned analysis results were reported for this arm only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1 up to start of LT (for those continuing in long-term) or up to 168 days after the last dose of study medication in the ST period (for those not entering in the long-term)

Notes:

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

Justification: Only summary statistics were planned for this endpoint.

|  |                              |  |  |  |
|--|------------------------------|--|--|--|
| <b>End point values</b>                              | SC Abatacept<br>Ages 6 to 17 |  |  |  |
| Subject group type                                   | Reporting group              |  |  |  |
| Number of subjects analysed                          | 171                          |  |  |  |
| Units: Subjects                                      |                              |  |  |  |
| # of subjects (6-17 yr) with +ve Imm.<br>Resp. in ST | 3                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Positive Immunogenicity Response in the Cumulative Period

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Positive Immunogenicity Response in the Cumulative Period |
|-----------------|---|

End point description:

Overall number of subjects with either a positive immunogenicity response for 'CTLA4 and possibly Ig' or 'Ig and/or Junction Region' relative to baseline. Sample draws for immunogenicity were scheduled at specific study days while on treatment for all subjects and at follow-up visits 28, 85, and 168 days after the last abatacept dose regardless of whether they discontinued early in the ST or LTE period, elected not to enter the LTE period, or completed both ST and LTE periods. Immunogenicity analysis population included all subjects who received at least one dose of study medication and who had at least 1 immunogenicity result reported after start of study medication.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 2 years

| <b>End point values</b>                            | SC Abatacept<br>Ages 6 to 17 | SC Abatacept<br>Ages 2 to 5 |  |  |
|--|------------------------------|-----------------------------|--|--|
| Subject group type                                 | Reporting group              | Reporting group             |  |  |
| Number of subjects analysed                        | 172                          | 46                          |  |  |
| Units: Subjects                                    |                              |                             |  |  |
| # of Subjects with +ve Imm. Resp in<br>Cum. Period | 8                            | 7                           |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 56 days after last dose ( up to 2 years)

Adverse event reporting additional description:

Safety population included all treated population who received at least one dose of study medication.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | SC Abatacept Ages 6 to 17 |
|-----------------------|---------------------------|

Reporting group description:

Subcutaneous (SC) abatacept administered by prefilled syringe (PFS) once weekly according to the following weight-tiered dosing regimen: 10 to less than (<) 25 kilogram (kg) (50 milligram [mg] in 0.4 milliliter [mL] PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | SC Abatacept Ages 2 to 5 |
|-----------------------|--------------------------|

Reporting group description:

All weight-tiered dosing groups receiving SC abatacept administered by prefilled syringe (PFS) once weekly according to weight-tiered dose regimen as follows: 10 to < 25kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS) and 50 kg (125 mg in 1 mL PFS).

| <b>Serious adverse events</b>                                       | SC Abatacept Ages 6 to 17 | SC Abatacept Ages 2 to 5 |  |
|---|---------------------------|--------------------------|--|
| Total subjects affected by serious adverse events                   |                           |                          |  |
| subjects affected / exposed   | 14 / 173 (8.09%)          | 5 / 46 (10.87%)          |  |
| number of deaths (all causes)                                       | 0                         | 0                        |  |
| number of deaths resulting from adverse events                      | 0                         | 0                        |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                          |  |
| Ovarian germ cell teratoma stage iii                                |                           |                          |  |
| subjects affected / exposed   | 1 / 173 (0.58%)           | 0 / 46 (0.00%)           |  |
| occurrences causally related to treatment / all                     | 0 / 1                     | 0 / 0                    |  |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                    |  |
| Injury, poisoning and procedural complications                      |                           |                          |  |
| Radius fracture   |                           |                          |  |
| subjects affected / exposed   | 1 / 173 (0.58%)           | 0 / 46 (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 / 173 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Nervous system disorders                             |                 |                |  |
| Syncope  |                 |                |  |
| subjects affected / exposed                          | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Autonomic nervous system imbalance                   |                 |                |  |
| subjects affected / exposed                          | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Febrile convulsion                                   |                 |                |  |
| subjects affected / exposed                          | 0 / 173 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Blood and lymphatic system disorders                 |                 |                |  |
| Anaemia  |                 |                |  |
| subjects affected / exposed                          | 1 / 173 (0.58%) | 0 / 46 (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                          | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Ear and labyrinth disorders                          |                 |                |  |
| Vertigo  |                 |                |  |
| subjects affected / exposed                          | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                           |                 |                |  |
| Abdominal pain                                       |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal and urinary disorders                     |                 |                |  |
| Nephrolithiasis                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Calculus urinary                                |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (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 |                 |                |  |
| Synovitis                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Tendon disorder                                 |                 |                |  |
| subjects affected / exposed                     | 0 / 173 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infections and infestations                     |                 |                |  |
| Pyelonephritis                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Sepsis  |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Appendicitis                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Pneumonia                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Abscess limb                                    |                 |                |  |
| subjects affected / exposed                     | 0 / 173 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cellulitis                                      |                 |                |  |
| subjects affected / exposed                     | 0 / 173 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Metabolism and nutrition disorders              |                 |                |  |
| Hypomagnesaemia                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 173 (0.58%) | 0 / 46 (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 %

| <b>Non-serious adverse events</b>                     | SC Abatacept Ages 6 to 17 | SC Abatacept Ages 2 to 5 |  |
|---|---------------------------|--------------------------|--|
| Total subjects affected by non-serious adverse events |                           |                          |  |
| subjects affected / exposed                           | 116 / 173 (67.05%)        | 42 / 46 (91.30%)         |  |
| Nervous system disorders                              |                           |                          |  |
| Headache  |                           |                          |  |
| subjects affected / exposed                           | 24 / 173 (13.87%)         | 6 / 46 (13.04%)          |  |
| occurrences (all)                                     | 35                        | 11                       |  |
| General disorders and administration site conditions  |                           |                          |  |
| Pyrexia   |                           |                          |  |
| subjects affected / exposed                           | 21 / 173 (12.14%)         | 15 / 46 (32.61%)         |  |
| occurrences (all)                                     | 35                        | 24                       |  |
| Blood and lymphatic system disorders                  |                           |                          |  |
| Anaemia   |                           |                          |  |
| subjects affected / exposed                           | 5 / 173 (2.89%)           | 3 / 46 (6.52%)           |  |
| occurrences (all)                                     | 5                         | 3                        |  |



|   |                   |                  |  |
|---|-------------------|------------------|--|
| Gastrointestinal disorders                      |                   |                  |  |
| Nausea  |                   |                  |  |
| subjects affected / exposed                     | 20 / 173 (11.56%) | 6 / 46 (13.04%)  |  |
| occurrences (all)                               | 26                | 7                |  |
| Vomiting  |                   |                  |  |
| subjects affected / exposed                     | 11 / 173 (6.36%)  | 6 / 46 (13.04%)  |  |
| occurrences (all)                               | 18                | 9                |  |
| Constipation                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 173 (0.58%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                               | 1                 | 5                |  |
| Diarrhoea                                       |                   |                  |  |
| subjects affected / exposed                     | 5 / 173 (2.89%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                               | 5                 | 3                |  |
| Abdominal pain                                  |                   |                  |  |
| subjects affected / exposed                     | 13 / 173 (7.51%)  | 4 / 46 (8.70%)   |  |
| occurrences (all)                               | 16                | 5                |  |
| Aphthous ulcer                                  |                   |                  |  |
| subjects affected / exposed                     | 3 / 173 (1.73%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                               | 7                 | 3                |  |
| Dental caries                                   |                   |                  |  |
| subjects affected / exposed                     | 7 / 173 (4.05%)   | 4 / 46 (8.70%)   |  |
| occurrences (all)                               | 11                | 9                |  |
| Respiratory, thoracic and mediastinal disorders |                   |                  |  |
| Cough   |                   |                  |  |
| subjects affected / exposed                     | 8 / 173 (4.62%)   | 9 / 46 (19.57%)  |  |
| occurrences (all)                               | 9                 | 12               |  |
| Infections and infestations                     |                   |                  |  |
| Nasopharyngitis                                 |                   |                  |  |
| subjects affected / exposed                     | 52 / 173 (30.06%) | 17 / 46 (36.96%) |  |
| occurrences (all)                               | 86                | 37               |  |
| Rhinitis  |                   |                  |  |
| subjects affected / exposed                     | 10 / 173 (5.78%)  | 8 / 46 (17.39%)  |  |
| occurrences (all)                               | 16                | 14               |  |
| Pharyngitis                                     |                   |                  |  |
| subjects affected / exposed                     | 11 / 173 (6.36%)  | 6 / 46 (13.04%)  |  |
| occurrences (all)                               | 13                | 7                |  |

|                                   |                   |                  |
|-----------------------------------|-------------------|------------------|
| Tonsillitis                       |                   |                  |
| subjects affected / exposed       | 6 / 173 (3.47%)   | 4 / 46 (8.70%)   |
| occurrences (all)                 | 9                 | 7                |
| Gastroenteritis                   |                   |                  |
| subjects affected / exposed       | 15 / 173 (8.67%)  | 6 / 46 (13.04%)  |
| occurrences (all)                 | 17                | 6                |
| Bronchitis                        |                   |                  |
| subjects affected / exposed       | 6 / 173 (3.47%)   | 4 / 46 (8.70%)   |
| occurrences (all)                 | 9                 | 5                |
| Conjunctivitis                    |                   |                  |
| subjects affected / exposed       | 7 / 173 (4.05%)   | 6 / 46 (13.04%)  |
| occurrences (all)                 | 8                 | 6                |
| Influenza                         |                   |                  |
| subjects affected / exposed       | 10 / 173 (5.78%)  | 3 / 46 (6.52%)   |
| occurrences (all)                 | 18                | 4                |
| Varicella                         |                   |                  |
| subjects affected / exposed       | 0 / 173 (0.00%)   | 3 / 46 (6.52%)   |
| occurrences (all)                 | 0                 | 3                |
| Scarlet fever                     |                   |                  |
| subjects affected / exposed       | 0 / 173 (0.00%)   | 3 / 46 (6.52%)   |
| occurrences (all)                 | 0                 | 3                |
| Molluscum contagiosum             |                   |                  |
| subjects affected / exposed       | 2 / 173 (1.16%)   | 3 / 46 (6.52%)   |
| occurrences (all)                 | 2                 | 3                |
| Upper respiratory tract infection |                   |                  |
| subjects affected / exposed       | 32 / 173 (18.50%) | 10 / 46 (21.74%) |
| occurrences (all)                 | 62                | 15               |
| Urinary tract infection           |                   |                  |
| subjects affected / exposed       | 10 / 173 (5.78%)  | 1 / 46 (2.17%)   |
| occurrences (all)                 | 13                | 1                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 05 February 2013 | The main reason of this amendment was to eliminate two questionnaires, the requirement of varicella vaccination prior to the enrollment in the study, the modification of the acceptable methods of contraception, and additional minor changes to the protocol.   |
| 14 February 2014 | The main reason of this amendment was to amend inclusion and exclusion criteria, revise pregnancy testing requirements, and to make additional minor changes to the protocol.  |
| 22 January 2015  | The main reason of this amendment was to clarify that the 7 days post dose follow up visit is performed as the early termination/final study completion visit, to update objectives/endpoints to align with the current regulatory view on long-term safety analysis, and to make other minor changes to the protocol. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported