



## Clinical trial results:

### A Phase IIb, Randomized, Multi-Center, Double-Blind, Dose-Ranging Study to Evaluate the Efficacy and Safety of Clazakizumab in Subjects With Moderate to Severe Active Rheumatoid Arthritis Who Have Experienced an Inadequate Response to TNF Inhibitors

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-003780-65 |
| Trial protocol           | IT HU          |
| Global end of trial date | 17 June 2015   |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 05 January 2019 |
| First version publication date | 05 January 2019 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | IM133-066 |
|-----------------------|-----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bristol-Myers Squibb  |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170   |
| Public contact               | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com              |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 17 June 2015 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 17 June 2015 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the efficacy of clazakizumab versus placebo on a background of methotrexate as assessed by change from baseline in DAS28-CRP at 12 weeks in subjects with moderate to severe active rheumatoid arthritis who have an inadequate response to TNF inhibitors (TNF-IR)

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                          | 13 January 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 38 |
| Country: Number of subjects enrolled | Canada: 5         |
| Country: Number of subjects enrolled | France: 2         |
| Country: Number of subjects enrolled | South Africa: 12  |
| Country: Number of subjects enrolled | Italy: 1          |
| Country: Number of subjects enrolled | Hungary: 22       |
| Country: Number of subjects enrolled | Mexico: 29        |
| Country: Number of subjects enrolled | Argentina: 18     |
| Country: Number of subjects enrolled | Japan: 16         |
| Worldwide total number of subjects   | 143               |
| EEA total number of subjects         | 25                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |     |
|--|-----|
| Newborns (0-27 days)                     | 0   |
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 114 |
| From 65 to 84 years                      | 28  |
| 85 years and over                        | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

216 subjects were enrolled. 143 subjects were randomized.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | 12 Week Double Blind Period |
| Is this the baseline period? | Yes                         |
| Allocation method            | Randomised - controlled     |
| Blinding used                | Double blind                |
| Roles blinded                | Subject, Investigator       |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | PBO + MTX |
|------------------|-----------|

Arm description:

Clazakizumab placebo SC every 4 weeks with background methotrexate

|  |                      |
|--|----------------------|
| Arm type                               | Placebo              |
| Investigational medicinal product name | Clazakizumab placebo |
| Investigational medicinal product code | BMS-945429 Placebo   |
| Other name                             |                      |
| Pharmaceutical forms                   | Injection            |
| Routes of administration               | Subcutaneous use     |

Dosage and administration details:

Clazakizumab placebo SC every 4 weeks with background methotrexate

|                  |          |
|------------------|----------|
| <b>Arm title</b> | C1 + MTX |
|------------------|----------|

Arm description:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Clazakizumab     |
| Investigational medicinal product code | BMS-945429       |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate

|                  |          |
|------------------|----------|
| <b>Arm title</b> | C5 + MTX |
|------------------|----------|

Arm description:

Clazakizumab 5 mg SC every 4 weeks with background methotrexate

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Clazakizumab     |
| Investigational medicinal product code | BMS-945429       |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Clazakizumab 5 mg SC every 4 weeks with background methotrexate

|  |                  |
|--|------------------|
| <b>Arm title</b>   | C25 + MTX        |
| Arm description:<br>Clazakizumab 25 mg SC every 4 weeks with background methotrexate |                  |
| Arm type   | Experimental     |
| Investigational medicinal product name   | Clazakizumab     |
| Investigational medicinal product code   | BMS-945429       |
| Other name   |                  |
| Pharmaceutical forms   | Injection        |
| Routes of administration   | Subcutaneous use |

Dosage and administration details:

Clazakizumab 25 mg SC every 4 weeks with background methotrexate

| <b>Number of subjects in period 1</b>    | PBO + MTX | C1 + MTX | C5 + MTX |
|--|-----------|----------|----------|
| Started                                  | 40        | 21       | 42       |
| Completed                                | 19        | 8        | 17       |
| Not completed                            | 21        | 13       | 25       |
| Adverse event, serious fatal             | 1         | -        | -        |
| Subject request to discontinue treatment | 1         | 1        | 2        |
| Consent withdrawn by subject             | 2         | 2        | 1        |
| Adverse event, non-fatal                 | -         | -        | -        |
| LTE -- other                             | 1         | 1        | -        |
| Completed DB and cont. to follow-up      | 14        | 8        | 16       |
| LTE -- sponsor reason                    | -         | -        | 1        |
| Completed DB, not dosed in LTE           | 1         | -        | -        |
| LTE -- withdrew consent                  | -         | -        | 1        |
| Lost to follow-up                        | -         | -        | 1        |
| Subject no longer meets study criteria   | -         | 1        | -        |
| Lack of efficacy                         | 1         | -        | 3        |

| <b>Number of subjects in period 1</b>    | C25 + MTX |
|--|-----------|
| Started                                  | 40        |
| Completed                                | 19        |
| Not completed                            | 21        |
| Adverse event, serious fatal             | -         |
| Subject request to discontinue treatment | 1         |
| Consent withdrawn by subject             | -         |
| Adverse event, non-fatal                 | 1         |
| LTE -- other                             | -         |
| Completed DB and cont. to follow-up      | 17        |

|  |   |
|--|---|
| LTE -- sponsor reason                  | - |
| Completed DB, not dosed in LTE         | - |
| LTE -- withdrew consent                | - |
| Lost to follow-up                      | - |
| Subject no longer meets study criteria | - |
| Lack of efficacy                       | 2 |

## Period 2

|                              |                                |
|------------------------------|--------------------------------|
| Period 2 title               | Open Label Long Term Extension |
| Is this the baseline period? | No                             |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

## Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | PBO + MTX |

Arm description:

Clazakizumab placebo SC every 4 weeks with background methotrexate

|  |                      |
|--|----------------------|
| Arm type                               | Placebo              |
| Investigational medicinal product name | Clazakizumab placebo |
| Investigational medicinal product code | BMS-945429 Placebo   |
| Other name                             |                      |
| Pharmaceutical forms                   | Injection            |
| Routes of administration               | Subcutaneous use     |

Dosage and administration details:

Clazakizumab placebo SC every 4 weeks with background methotrexate

|                  |          |
|------------------|----------|
| <b>Arm title</b> | C1 + MTX |
|------------------|----------|

Arm description:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate (n = 20)

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Clazakizumab     |
| Investigational medicinal product code | BMS-945429       |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate

|                  |          |
|------------------|----------|
| <b>Arm title</b> | C5 + MTX |
|------------------|----------|

Arm description:

Clazakizumab 5 mg SC every 4 weeks with background methotrexate

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |                  |
|---|------------------|
| Investigational medicinal product name                          | Clazakizumab     |
| Investigational medicinal product code                          | BMS-945429       |
| Other name  |                  |
| Pharmaceutical forms  | Injection        |
| Routes of administration  | Subcutaneous use |
| Dosage and administration details:                              |                  |
| Clazakizumab 5 mg SC every 4 weeks with background methotrexate |                  |
| <b>Arm title</b>  | C25 + MTX        |

Arm description:

Clazakizumab 25 mg SC every 4 weeks with background methotrexate

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Clazakizumab     |
| Investigational medicinal product code | BMS-945429       |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Clazakizumab 25 mg SC every 4 weeks with background methotrexate

| <b>Number of subjects in period 2</b> | PBO + MTX | C1 + MTX | C5 + MTX |
|---------------------------------------|-----------|----------|----------|
| Started                               | 19        | 8        | 17       |
| Completed                             | 0         | 1        | 0        |
| Not completed                         | 19        | 7        | 17       |
| Consent withdrawn by subject          | 1         | -        | -        |
| Adverse event, non-fatal              | -         | -        | -        |
| Ongoing in LTE as of Apr2015          | 3         | 1        | 2        |
| Sponsor reason                        | 15        | 6        | 15       |

| <b>Number of subjects in period 2</b> | C25 + MTX |
|---------------------------------------|-----------|
| Started                               | 19        |
| Completed                             | 1         |
| Not completed                         | 18        |
| Consent withdrawn by subject          | -         |
| Adverse event, non-fatal              | 1         |
| Ongoing in LTE as of Apr2015          | 4         |
| Sponsor reason                        | 13        |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | PBO + MTX |
| Reporting group description:                                       |           |
| Clazakizumab placebo SC every 4 weeks with background methotrexate |           |
| Reporting group title  | C1 + MTX  |
| Reporting group description:                                       |           |
| Clazakizumab 1 mg SC every 4 weeks with background methotrexate    |           |
| Reporting group title  | C5 + MTX  |
| Reporting group description:                                       |           |
| Clazakizumab 5 mg SC every 4 weeks with background methotrexate    |           |
| Reporting group title  | C25 + MTX |
| Reporting group description:                                       |           |
| Clazakizumab 25 mg SC every 4 weeks with background methotrexate   |           |

| Reporting group values                                | PBO + MTX | C1 + MTX | C5 + MTX |
|---|-----------|----------|----------|
| Number of subjects                                    | 40        | 21       | 42       |
| 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)                                 | 0         | 0        | 0        |
| Adolescents (12-17 years)                             | 0         | 0        | 0        |
| Adults (18-64 years)                                  | 32        | 15       | 35       |
| From 65-84 years                                      | 8         | 6        | 6        |
| 85 years and over                                     | 0         | 0        | 1        |
| Age Continuous<br>Units: years                        |           |          |          |
| arithmetic mean                                       | 54.4      | 55.8     | 53.4     |
| standard deviation                                    | ± 11.21   | ± 11.20  | ± 13.75  |
| Gender Categorical<br>Units: Subjects                 |           |          |          |
| Female  | 35        | 18       | 33       |
| Male  | 5         | 3        | 9        |
| Race (NIH/OMB)<br>Units: Subjects                     |           |          |          |
| White   | 30        | 18       | 34       |
| Black or African American                             | 1         | 0        | 2        |
| Asian   | 5         | 3        | 5        |
| Other   | 4         | 0        | 1        |
| Ethnicity (NIH/OMB)<br>Units: Subjects                |           |          |          |
| Hispanic/Latino                                       | 4         | 1        | 4        |
| Not Hispanic/Latino                                   | 20        | 12       | 21       |



|              |    |   |    |
|--------------|----|---|----|
| Not reported | 16 | 8 | 17 |
|--------------|----|---|----|

| Reporting group values                                | C25 + MTX | Total |  |
|---|-----------|-------|--|
| Number of subjects                                    | 40        | 143   |  |
| Age Categorical<br>Units: Subjects                    |           |       |  |
| In utero  | 0         | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0         | 0     |  |
| Newborns (0-27 days)                                  | 0         | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0         | 0     |  |
| Children (2-11 years)                                 | 0         | 0     |  |
| Adolescents (12-17 years)                             | 0         | 0     |  |
| Adults (18-64 years)                                  | 32        | 114   |  |
| From 65-84 years                                      | 8         | 28    |  |
| 85 years and over                                     | 0         | 1     |  |
| Age Continuous<br>Units: years                        |           |       |  |
| arithmetic mean                                       | 52.6      |       |  |
| standard deviation                                    | ± 13.21   | -     |  |
| Gender Categorical<br>Units: Subjects                 |           |       |  |
| Female  | 35        | 121   |  |
| Male  | 5         | 22    |  |
| Race (NIH/OMB)<br>Units: Subjects                     |           |       |  |
| White   | 33        | 115   |  |
| Black or African American                             | 0         | 3     |  |
| Asian   | 4         | 17    |  |
| Other   | 3         | 8     |  |
| Ethnicity (NIH/OMB)<br>Units: Subjects                |           |       |  |
| Hispanic/Latino                                       | 5         | 14    |  |
| Not Hispanic/Latino                                   | 17        | 70    |  |
| Not reported  | 18        | 59    |  |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | PBO + MTX |
| Reporting group description:<br>Clazakizumab placebo SC every 4 weeks with background methotrexate       |           |
| Reporting group title  | C1 + MTX  |
| Reporting group description:<br>Clazakizumab 1 mg SC every 4 weeks with background methotrexate          |           |
| Reporting group title  | C5 + MTX  |
| Reporting group description:<br>Clazakizumab 5 mg SC every 4 weeks with background methotrexate          |           |
| Reporting group title  | C25 + MTX |
| Reporting group description:<br>Clazakizumab 25 mg SC every 4 weeks with background methotrexate         |           |
| Reporting group title  | PBO + MTX |
| Reporting group description:<br>Clazakizumab placebo SC every 4 weeks with background methotrexate       |           |
| Reporting group title  | C1 + MTX  |
| Reporting group description:<br>Clazakizumab 1 mg SC every 4 weeks with background methotrexate (n = 20) |           |
| Reporting group title  | C5 + MTX  |
| Reporting group description:<br>Clazakizumab 5 mg SC every 4 weeks with background methotrexate          |           |
| Reporting group title  | C25 + MTX |
| Reporting group description:<br>Clazakizumab 25 mg SC every 4 weeks with background methotrexate         |           |

### Primary: Mean Change from Baseline in Disease Activity Score in 28 joints - C-reactive protein (DAS28-CRP) at Week 12

|  |  |
|--|--|
| End point title  | Mean Change from Baseline in Disease Activity Score in 28 joints - C-reactive protein (DAS28-CRP) at Week 12 |
| End point description:<br>The DAS using the 28-count subsets of tender/painful joints and swollen joints, together with CRP to derive the DAS28-CRP, was calculated using the following formula: $\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP} + 1) + 0.014 \cdot \text{GH} + 0.96$ ; where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, and CRP is in mg/L. A score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission. |  |
| End point type   | Primary  |
| End point timeframe:<br>Day 1 to Week 12   |  |

| End point values                 | PBO + MTX        | C1 + MTX         | C5 + MTX         | C25 + MTX        |
|----------------------------------|------------------|------------------|------------------|------------------|
| Subject group type               | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed      | 34               | 15               | 35               | 37               |
| Units: Score                     |                  |                  |                  |                  |
| arithmetic mean (standard error) | -0.75 (± 0.2249) | -1.10 (± 0.3303) | -2.10 (± 0.2209) | -2.43 (± 0.2190) |

## Statistical analyses

|   |                                   |
|---|-----------------------------------|
| <b>Statistical analysis title</b>       | P-value of (C1+MTX) vs (PBO +MTX) |
| Comparison groups                       | PBO + MTX v C1 + MTX              |
| Number of subjects included in analysis | 49                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.3846 <sup>[1]</sup>           |
| Method                                  | Mixed models analysis             |

Notes:

[1] - Based on the linear mixed model analysis and a hierarchical testing procedure implemented to control the overall type I error rate at 0.05 levels (one-sided)

|   |                                   |
|---|-----------------------------------|
| <b>Statistical analysis title</b>       | P-value of (C5+MTX) vs (PBO +MTX) |
| Comparison groups                       | PBO + MTX v C5 + MTX              |
| Number of subjects included in analysis | 69                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | < 0.001 <sup>[2]</sup>            |
| Method                                  | Mixed models analysis             |

Notes:

[2] - Based on the linear mixed model analysis and a hierarchical testing procedure implemented to control the overall type I error rate at 0.05 levels (one-sided)

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | P-value of (C25+MTX) vs (PBO +MTX) |
| Comparison groups                       | PBO + MTX v C25 + MTX              |
| Number of subjects included in analysis | 71                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | < 0.001 <sup>[3]</sup>             |
| Method                                  | Mixed models analysis              |

Notes:

[3] - Based on the linear mixed model analysis and a hierarchical testing procedure implemented to control the overall type I error rate at 0.05 levels (one-sided)

## Secondary: Percentage of Subjects Meeting the Criteria of the American College of Rheumatology for 20%/50%/70% Improvement (ACR 20/50/70) Responses at Week 12

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Meeting the Criteria of the American College of Rheumatology for 20%/50%/70% Improvement (ACR 20/50/70) Responses at Week 12 |
|-----------------|---|

End point description:

The ACR x is based on x% improvement (compared with baseline values) in tender and swollen joint counts and on x% improvement in 3 of the remaining 5 core set measures (participant global assessment of pain, participant global assessment of disease activity, physician global assessment of

disease activity, participant assessment of physical function) and 1 acute phase reactant value. x = 20, 50,70 for ACR 20/50/70

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values                 | PBO + MTX           | C1 + MTX           | C5 + MTX            | C25 + MTX           |
|----------------------------------|---------------------|--------------------|---------------------|---------------------|
| Subject group type               | Reporting group     | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed      | 40                  | 21                 | 42                  | 40                  |
| Units: Percentage                |                     |                    |                     |                     |
| number (confidence interval 95%) |                     |                    |                     |                     |
| ACR 20                           | 27.5 (13.7 to 41.3) | 14.3 (3.0 to 36.3) | 50.0 (34.9 to 65.1) | 47.5 (32.0 to 63.0) |
| ACR 50                           | 7.5 (1.6 to 20.4)   | 14.3 (3.0 to 36.3) | 21.4 (9.0 to 33.8)  | 22.5 (9.6 to 35.4)  |
| ACR 70                           | 2.5 (0.1 to 13.2)   | 4.8 (0.1 to 23.8)  | 9.5 (2.7 to 22.6)   | 15.0 (3.9 to 26.1)  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Clinical Disease Activity Index (CDAI) Remission Responder (CDAI ≤ 2.8) at Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with Clinical Disease Activity Index (CDAI) Remission Responder (CDAI ≤ 2.8) at Week 12 |
|-----------------|--|

End point description:

Clinical Disease Activity Index (CDAI) is calculated as the simple linear sum of the outcome parameters: tender joint count (TJC) and swollen joint count (SJC) based on a 28-joint assessment, patient global assessment of disease activity (PGA: VAS 0–10 cm), and physician global assessment of disease activity (EGA: VAS 0–10 cm): CDAI = TJC28 + SJC28 + PGA + EGA. CDAI total score=0-76. CDAI ≤2.8 indicates disease remission, >2.8 to 10=low DA, >10 to 22=moderate DA, and >22=high DA. CDAI Remission responder is defined as a CDAI score less than or equal to 2.8.

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

End point timeframe:

At week 12

| End point values                 | PBO + MTX         | C1 + MTX          | C5 + MTX            | C25 + MTX         |
|----------------------------------|-------------------|-------------------|---------------------|-------------------|
| Subject group type               | Reporting group   | Reporting group   | Reporting group     | Reporting group   |
| Number of subjects analysed      | 40                | 21                | 42                  | 40                |
| Units: Percentage                |                   |                   |                     |                   |
| number (confidence interval 95%) | 2.5 (0.1 to 13.2) | 9.5 (1.2 to 30.4) | 9999 (9999 to 9999) | 7.5 (1.6 to 20.4) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI), SDAI ≤ 3.3, at week 12

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI), SDAI ≤ 3.3, at week 12 |
|-----------------|---|

End point description:

The SDAI is the simple linear sum of 5 outcome parameters: tender joint count (TJC) and swollen joint count (SJC) (based on a 28-joint assessment); patient's and physician's global assessments of disease activity (assessed on 0-10 cm visual analog scale, on which higher scores=greater affection due to disease activity); and C-reactive protein level (mg/dL). SDAI total score=0-86. SDAI ≤3.3 indicates disease remission, >3.4 to 11=low disease activity, >11 to 26=moderate disease activity, and >26=high disease activity. TJC is assessed and recorded at each visit, with no swelling=0, swelling=1. SJC is assessed through identification of joints that are painful under pressure or to passive motion. TJC is recorded on the joint assessment form at each visit, with no tenderness =0, tenderness = 1. Higher score indicates worst health condition.

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

End point timeframe:

At week 12

| End point values                 | PBO + MTX         | C1 + MTX          | C5 + MTX            | C25 + MTX         |
|----------------------------------|-------------------|-------------------|---------------------|-------------------|
| Subject group type               | Reporting group   | Reporting group   | Reporting group     | Reporting group   |
| Number of subjects analysed      | 40                | 21                | 42                  | 40                |
| Units: Percentage                |                   |                   |                     |                   |
| number (confidence interval 95%) | 2.5 (0.1 to 13.2) | 9.5 (1.2 to 30.4) | 9999 (9999 to 9999) | 7.5 (1.6 to 20.4) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects achieving Boolean Remission (Boolean Remission Rate) at Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects achieving Boolean Remission (Boolean Remission Rate) at Week 12 |
|-----------------|--|

End point description:

Remission by Boolean-based definition: Subject must satisfy all of the followings: TJC28 ≤1; SJC28≤1; PGA≤1; CRP≤1 mg/dL where tender joint count (TJC) and swollen joint count (SJC) are based on a 28-joint assessment, patient global assessment of disease activity (PGA: VAS 0–10 cm), physician global assessment of disease activity (EGA: VAS 0–10 cm) and C-reactive protein (CRP in mg/dL). Higher scores indicate worst health condition

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

End point timeframe:

Week 12

| End point values                 | PBO + MTX         | C1 + MTX          | C5 + MTX          | C25 + MTX         |
|----------------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type               | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed      | 40                | 21                | 42                | 40                |
| Units: Percentage                |                   |                   |                   |                   |
| number (confidence interval 95%) | 5.0 (0.6 to 16.9) | 4.8 (0.1 to 23.8) | 2.4 (0.1 to 12.6) | 5.0 (0.6 to 16.9) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Health assessment questionnaire disability index (HAQ-DI) change from baseline of at least 0.22 units at Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with Health assessment questionnaire disability index (HAQ-DI) change from baseline of at least 0.22 units at Week 12 |
|-----------------|--|

End point description:

HAQ responder is defined as a reduction of at least 0.22 units from baseline in score on the Health Assessment Questionnaire Disability Index (HAQ-DI), which assesses patients' functional ability by rating their abilities over the previous week. The HAQ-DI includes at least 2 questions from each of 8 categories: dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities. Patients rate difficulty performing specific tasks: 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The sum of the categories score (the highest scored item in the category) is divided by the number of categories answered, yielding a score from 0-3. When aids, devices, or help is indicated by the patient, the score for the category item is raised from a 0 or a 1 to a 2, but if the patient's highest score for a subcategory is a 3, it stays a 3.

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

End point timeframe:

Day 1 to Week 12

| End point values                 | PBO + MTX           | C1 + MTX           | C5 + MTX            | C25 + MTX           |
|----------------------------------|---------------------|--------------------|---------------------|---------------------|
| Subject group type               | Reporting group     | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed      | 40                  | 21                 | 42                  | 40                  |
| Units: Percentage                |                     |                    |                     |                     |
| number (confidence interval 95%) | 47.5 (32.0 to 63.0) | 19.0 (5.4 to 41.9) | 47.6 (32.5 to 62.7) | 50.0 (34.5 to 65.5) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With DAS28- Erythrocyte sedimentation rate (ESR) <2.6 at Week 12

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With DAS28- Erythrocyte sedimentation rate (ESR) <2.6 at Week 12 |
|-----------------|---|

End point description:

The Disease Activity Score (DAS) using the 28-count subsets of tender/painful joints and swollen joints, together with erythrocyte sedimentation rate ESR, to derive the, DAS28-ESR, was calculated using the

following formula:  $\text{DAS28-ESR} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot \text{GH}$  ; where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, ESR is in mm/hour. DAS28-ESR scores could range from 0 to 10, where higher scores represented higher disease activity. DAS28-ESR score less than or equal to ( $\leq$ ) 3.2 indicates LDA, DAS28-ESR score greater than ( $>$ ) 3.2 indicates moderate to high disease activity, and DAS28-ESR less than ( $<$ ) 2.6 indicates remission.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| At week 12           |           |

| End point values                 | PBO + MTX         | C1 + MTX          | C5 + MTX          | C25 + MTX          |
|----------------------------------|-------------------|-------------------|-------------------|--------------------|
| Subject group type               | Reporting group   | Reporting group   | Reporting group   | Reporting group    |
| Number of subjects analysed      | 40                | 21                | 42                | 40                 |
| Units: Percentage                |                   |                   |                   |                    |
| number (confidence interval 95%) | 2.5 (0.1 to 13.2) | 4.8 (0.1 to 23.8) | 7.1 (1.5 to 19.5) | 15.0 (3.9 to 26.1) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Who Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria, DAS28<2.6, at Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Who Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria, DAS28<2.6, at Week 12 |
|-----------------|--|

End point description:

The DAS using the 28-count subsets of tender/painful joints and swollen joints, together with CRP to derive the DAS28-CRP, was calculated using the following formula:  $\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP}+1) + 0.014 \cdot \text{GH} + 0.96$ ; where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, and CRP is in mg/L. A score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| At week 12           |           |

| End point values                 | PBO + MTX         | C1 + MTX          | C5 + MTX           | C25 + MTX          |
|----------------------------------|-------------------|-------------------|--------------------|--------------------|
| Subject group type               | Reporting group   | Reporting group   | Reporting group    | Reporting group    |
| Number of subjects analysed      | 40                | 21                | 42                 | 40                 |
| Units: Percentage                |                   |                   |                    |                    |
| number (confidence interval 95%) | 5.0 (0.6 to 16.9) | 9.5 (1.2 to 30.4) | 14.3 (3.7 to 24.9) | 15.0 (3.9 to 26.1) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with Adverse Events

|                 |  |
|-----------------|--|
| End point title | Number of subjects with Adverse Events |
|-----------------|--|

End point description:

Adverse Events include deaths, serious adverse events, related serious adverse events, discontinuations due to serious adverse events, adverse events, related adverse events and discontinuations due to adverse events

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

End point timeframe:

From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier.

| End point values              | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type            | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed   | 40              | 21              | 42              | 40              |
| Units: Subjects               |                 |                 |                 |                 |
| Deaths                        | 1               | 0               | 0               | 0               |
| Serious Adverse Events (SAEs) | 1               | 0               | 0               | 1               |
| Related SAEs                  | 1               | 0               | 0               | 0               |
| Discontinued due to SAEs      | 0               | 0               | 0               | 0               |
| AEs                           | 14              | 5               | 24              | 28              |
| Related AEs                   | 5               | 3               | 9               | 16              |
| Discontinued due to AEs       | 0               | 0               | 0               | 1               |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Vital Signs - Sitting Systolic Blood Pressure

|                 |   |
|-----------------|---|
| End point title | Vital Signs - Sitting Systolic Blood Pressure |
|-----------------|---|

End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

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

End point timeframe:

Screening Visit 1 to Week 12



| End point values                              | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type                            | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                   | 40              | 21              | 42              | 40              |
| Units: mmHg                                   |                 |                 |                 |                 |
| arithmetic mean (standard deviation)          |                 |                 |                 |                 |
| Screening Visit #1 (N =39,21,42,40)           | 125.9 (± 14.10) | 125.4 (± 15.45) | 126.0 (± 12.10) | 126.7 (± 16.37) |
| Screening Visit # 2 (N = 3,3,2, Not reported) | 121.3 (± 12.06) | 122.0 (± 19.08) | 121.5 (± 6.36)  | 9999 (± 9999)   |
| Day 1 Pre (N = 39, 21, 42, 40)                | 123.8 (± 12.67) | 124.7 (± 15.44) | 125.8 (± 12.94) | 123.3 (± 13.04) |
| Day 1 1 Hr Post (N = 38,21,42,40)             | 123.1 (± 12.36) | 121.4 (± 18.56) | 123.9 (± 13.86) | 119.2 (± 12.62) |
| Day 1 2 hr Post (N = 39,20,42,40)             | 124.1 (± 15.24) | 124.7 (± 11.49) | 123.6 (± 11.75) | 120.9 (± 11.87) |
| Week 1 (N = 40,20,41,40)                      | 123.6 (± 16.54) | 124.7 (± 13.89) | 126.9 (± 13.56) | 125.4 (± 15.25) |
| Week 2 (N = 40,20,40,40)                      | 122.9 (± 13.08) | 121.5 (± 15.81) | 121.7 (± 13.28) | 124.4 (± 16.25) |
| Week 4 (N = 38,17,39,38)                      | 122.3 (± 12.27) | 122.1 (± 15.27) | 127.1 (± 13.31) | 123.4 (± 16.25) |
| Week 8 (N = 34,17,38,37)                      | 123.5 (± 10.66) | 121.5 (± 15.26) | 127.9 (± 11.48) | 128.6 (± 14.80) |
| Week 12 ( N = 27,14,25,27)                    | 123.4 (± 11.75) | 123.6 (± 12.31) | 128.2 (± 13.65) | 127.0 (± 15.38) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vital Signs -- Sitting Diastolic Blood Pressure

|                 |   |
|-----------------|---|
| End point title | Vital Signs -- Sitting Diastolic Blood Pressure |
|-----------------|---|

End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

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

End point timeframe:

Screening visit 1 to Week 12

| End point values                               | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type                             | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                    | 40              | 21              | 42              | 40              |
| Units: mmHg                                    |                 |                 |                 |                 |
| arithmetic mean (standard deviation)           |                 |                 |                 |                 |
| Screening visit # 1 (N= 39,21,42,40)           | 81.3 (± 8.55)   | 78.7 (± 9.28)   | 77.5 (± 7.27)   | 78.4 (± 8.88)   |
| Screening visit # 2 (N = 3, 3,2, not reported) | 72.3 (± 9.71)   | 75.7 (± 4.04)   | 83.0 (± 1.41)   | 9999 (± 9999)   |
| Day 1 Pre (N = 39,21,42,40)                    | 77.7 (± 8.02)   | 74.9 (± 9.37)   | 78.3 (± 9.23)   | 76.0 (± 8.13)   |
| Day 1 1 Hr Post (N = 38,21,42,40)              | 77.0 (± 7.53)   | 73.5 (± 10.93)  | 76.3 (± 9.86)   | 73.0 (± 7.90)   |
| Day 1 2 Hr Post (N = 39,20,42,40)              | 77.1 (± 8.94)   | 74.0 (± 7.00)   | 75.9 (± 8.89)   | 74.9 (± 6.49)   |
| Week 1 (N = 40,20,41,40)                       | 76.9 (± 8.56)   | 74.6 (± 9.04)   | 78.2 (± 8.48)   | 76.7 (± 9.69)   |
| Week 2 (N = 40,20,40,40)                       | 76.3 (± 7.98)   | 74.8 (± 10.18)  | 74.5 (± 8.76)   | 75.7 (± 10.53)  |
| Week 4 (N = 38, 17, 39, 38)                    | 75.1 (± 9.26)   | 73.6 (± 7.91)   | 80.7 (± 8.25)   | 78.7 (± 10.10)  |
| Week 8 (N = 34,17,38,37)                       | 75.9 (± 8.11)   | 73.7 (± 10.65)  | 79.2 (± 8.24)   | 78.9 (± 9.35)   |
| Week 12 ( N = 27,14,25,27)                     | 77.3 (± 7.51)   | 71.3 (± 5.66)   | 78.4 (± 9.40)   | 76.1 (± 9.17)   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vital Signs -- Sitting Heart Rate

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Vital Signs -- Sitting Heart Rate |
|-----------------|-----------------------------------|

End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

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

End point timeframe:

Screening visit 1 to Week 12

| End point values                              | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type                            | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                   | 40              | 21              | 42              | 40              |
| Units: bpm                                    |                 |                 |                 |                 |
| arithmetic mean (standard deviation)          |                 |                 |                 |                 |
| Screening visit #1 (N = 39, 21, 42, 40)       | 77.6 (± 10.51)  | 75.0 (± 10.23)  | 75.2 (± 12.82)  | 76.6 (± 9.21)   |
| Screening visit #2 ( N = 3,3,2, Not reported) | 85.7 (± 12.01)  | 69.3 (± 16.65)  | 84.0 (± 8.49)   | 9999 (± 9999)   |
| Day 1 Pre (N = 39,21,42,40)                   | 76.6 (± 10.41)  | 76.2 (± 9.80)   | 76.5 (± 9.33)   | 77.5 (± 10.19)  |
| Day 1 1 Hr Post (N = 38,21,42,40)             | 74.4 (± 9.99)   | 74.4 (± 10.61)  | 77.1 (± 8.58)   | 75.3 (± 8.92)   |
| Day 1 2 Hr Post (N = 39,20,42,40)             | 75.7 (± 9.94)   | 73.3 (± 10.22)  | 75.6 (± 7.50)   | 75.9 (± 9.27)   |
| Week 1 (N = 40, 20, 41, 40)                   | 76.8 (± 9.50)   | 70.9 (± 11.16)  | 73.6 (± 8.37)   | 72.0 (± 9.06)   |
| Week 2 (N = 40, 20, 40, 40)                   | 75.9 (± 8.42)   | 72.7 (± 10.18)  | 71.9 (± 8.68)   | 73.7 (± 9.26)   |
| Week 4 ( N = 38,17,39,38)                     | 74.7 (± 9.64)   | 73.8 (± 13.06)  | 74.9 (± 9.45)   | 73.3 (± 11.17)  |
| Week 8 (N = 34,17,38,37)                      | 76.0 (± 8.73)   | 73.0 (± 11.42)  | 74.1 (± 8.02)   | 74.4 (± 10.83)  |
| Week 12 (N = 27,14,25,27)                     | 75.1 (± 11.12)  | 72.7 (± 9.02)   | 75.0 (± 7.90)   | 73.9 (± 9.91)   |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Vital Signs -- Sitting Respiration rate

|                 |   |
|-----------------|---|
| End point title | Vital Signs -- Sitting Respiration rate |
|-----------------|---|

End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

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

End point timeframe:

Screening visit 1 to Week 12

| End point values                              | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type                            | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                   | 40              | 21              | 42              | 40              |
| Units: per min                                |                 |                 |                 |                 |
| arithmetic mean (standard deviation)          |                 |                 |                 |                 |
| Screening visit # 1 (N = 38,21,42,40)         | 16.2 (± 2.45)   | 15.4 (± 2.42)   | 16.2 (± 2.22)   | 16.2 (± 2.03)   |
| Screening visit # 2 (N = 3,3,2, Not reported) | 15.0 (± 2.65)   | 17.7 (± 5.13)   | 20.0 (± 0.00)   | 9999 (± 9999)   |
| Day 1 Pre ( N = 39,21,41,40)                  | 16.6 (± 2.37)   | 15.9 (± 2.61)   | 16.6 (± 2.08)   | 16.3 (± 2.41)   |
| Day 1 1 Hr Post (N = 38,21,41,40)             | 16.4 (± 2.56)   | 15.8 (± 2.11)   | 16.4 (± 2.15)   | 16.1 (± 1.94)   |
| Day 1 2 hr Post (N = 39,20,41,40)             | 16.5 (± 2.45)   | 15.5 (± 2.35)   | 16.6 (± 2.27)   | 16.1 (± 1.95)   |
| Week 1 (N = 40,20,41,40)                      | 16.5 (± 2.21)   | 16.0 (± 2.36)   | 16.5 (± 2.28)   | 15.8 (± 2.80)   |
| Week 2 ( N = 40,20,40,40)                     | 16.5 (± 2.52)   | 15.9 (± 2.20)   | 16.4 (± 2.35)   | 16.1 (± 2.37)   |
| Week 4 (N = 38,17,39,38)                      | 16.9 (± 2.50)   | 16.8 (± 2.88)   | 16.3 (± 1.89)   | 16.1 (± 2.41)   |
| Week 8 (N = 34, 17, 38, 37)                   | 16.7 (± 2.40)   | 16.9 (± 2.99)   | 16.2 (± 2.03)   | 16.1 (± 2.21)   |
| Week 12 (N = 27,14, 25 ,27)                   | 17.3 (± 2.14)   | 16.9 (± 2.54)   | 16.4 (± 2.06)   | 16.0 (± 2.18)   |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Vital signs -- Sitting temperature

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Vital signs -- Sitting temperature |
|-----------------|------------------------------------|

End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Screening visit 1 to Week 12 |           |

| End point values                              | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type                            | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                   | 40              | 21              | 42              | 40              |
| Units: degree C                               |                 |                 |                 |                 |
| arithmetic mean (standard deviation)          |                 |                 |                 |                 |
| Screening Visit #1 (N = 39,21,42,40)          | 36.43 (± 0.326) | 36.44 (± 0.291) | 36.29 (± 0.582) | 36.42 (± 0.372) |
| Screening visit # 2 (N = 3,3,2, Not reported) | 36.37 (± 0.115) | 36.57 (± 0.252) | 36.65 (± 0.071) | 9999 (± 9999)   |
| Day 1 Pre (N = 39,21,42,40)                   | 36.47 (± 0.294) | 36.49 (± 0.399) | 36.36 (± 0.561) | 36.27 (± 0.504) |
| Day 1 1 Hr Post (N = 38,21,42,40)             | 36.46 (± 0.308) | 36.55 (± 0.364) | 36.40 (± 0.449) | 36.28 (± 0.522) |
| Day 1 2 Hr Post (N = 39,20,42,40)             | 36.46 (± 0.264) | 36.52 (± 0.341) | 36.39 (± 0.524) | 36.31 (± 0.402) |
| Week 1 (N = 40,20,41,40)                      | 36.42 (± 0.365) | 36.41 (± 0.380) | 36.33 (± 0.420) | 36.29 (± 0.498) |
| Week 2 (N = 40,20,40,40)                      | 36.43 (± 0.387) | 36.35 (± 0.389) | 36.32 (± 0.533) | 36.26 (± 0.546) |
| Week 4 (N = 38,17,39, 38)                     | 36.37 (± 0.342) | 36.46 (± 0.453) | 36.31 (± 0.526) | 36.26 (± 0.493) |
| Week 8 (N = 34,17,38,37)                      | 36.44 (± 0.341) | 36.35 (± 0.332) | 36.32 (± 0.477) | 36.36 (± 0.396) |
| Week 12 (N = 27,14,25,27)                     | 36.52 (± 0.414) | 36.36 (± 0.282) | 36.38 (± 0.512) | 36.36 (± 0.465) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Marked Laboratory Abnormality -- Hematology I

|   |   |
|---|---|
| End point title   | Marked Laboratory Abnormality -- Hematology I |
| End point description:  |   |
| ERYTHROCYTE/PLATELET ATTRIBUTES: HEMOGLOBIN HB G/L LOW IF < 80 FOR FEMALES LOW IF < 90 FOR MALES; HIGH IF > 185 FOR BOTH FEMALES AND MALES; PLATELET COUNT PLAT X10*9 C/L LOW IF VALUE < 50 |   |
| End point type  | Secondary                                     |
| End point timeframe:  |   |
| From 1st dose in double blind period up to 150 days post the last dose if subject discontinued study medication, or the first dose date in LTE period, whichever is the earlier.            |   |

| End point values            | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40              | 21              | 42              | 40              |
| Units: Percentage           |                 |                 |                 |                 |
| number (not applicable)     |                 |                 |                 |                 |
| Hemoglobin Low              | 0               | 0               | 0               | 0               |
| Hemoglobin High             | 0               | 0               | 0               | 0               |
| Platelet Count, Low         | 0               | 0               | 0               | 2.5             |
| Platelet Count, High        | 9999            | 9999            | 9999            | 9999            |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Marked Laboratory Abnormality -- Hematology II

|  |  |
|--|--|
| End point title  | Marked Laboratory Abnormality -- Hematology II |
| End point description:<br>QUANTITATIVE WBC:LEUKOCYTES WBC X10*9 C/L LOW IF VALUE < 2.0; WBC DIFFERENTIAL COUNT; NEUTROPHILS (ABSOLUTE) NEUTA X10*9 C/L LOW IF ABSOLUTE COUNT < 1.0; LYMPHOCYTES (ABSOLUTE) LYMPA X10*9 C/L LOW IF ABSOLUTE COUNT < 1.0 |  |
| End point type   | Secondary                                      |
| End point timeframe:<br>From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier.  |  |

| End point values            | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40              | 21              | 42              | 40              |
| Units: Percentage           |                 |                 |                 |                 |
| number (not applicable)     |                 |                 |                 |                 |
| Quant. WBC Leukocytes Low   | 0               | 0               | 0               | 0               |
| Quant. WBC Leukocytes High  | 9999            | 9999            | 9999            | 9999            |
| Lymphocytes (Abs.) Low      | 7.5             | 5.0             | 16.7            | 10.0            |
| Lymphocytes (Abs.) High     | 9999            | 9999            | 9999            | 9999            |
| Neutrophils (Abs.) Low      | 0               | 5.0             | 0               | 0               |
| Neutrophils (Abs.) High     | 9999            | 9999            | 9999            | 9999            |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Marked Laboratory Abnormality -- Liver and Kidney Function

|                 |  |
|-----------------|--|
| End point title | Marked Laboratory Abnormality -- Liver and Kidney Function |
|-----------------|--|

End point description:

LIVER FUNCTION TESTS: ALKALINE PHOSPHATASE (ALP) ALP U/L HIGH IF VALUE > 3X ULN; ASPARTATE AMINOTRANSFERASE (AST) AST U/L HIGH IF VALUE > 5X ULN; ALANINE AMINOTRANSFERASE (ALT) ALT U/L HIGH IF VALUE > 5X ULN; BILIRUBIN, TOTAL TBILI UMOL/L HIGH IF VALUE > 2.0X ULN; BILIRUBIN, DIRECT DBILI UMOL/L HIGH IF VALUE >= 17.1

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

End point timeframe:

From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier.

| End point values                      | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|---------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                    | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed           | 40              | 21              | 42              | 40              |
| Units: Percentage                     |                 |                 |                 |                 |
| number (not applicable)               |                 |                 |                 |                 |
| Alanine Aminotransferase (ALT) Low    | 9999            | 9999            | 9999            | 9999            |
| Alanine Aminotransferase (ALT) High   | 0               | 0               | 0               | 0               |
| Alkaline Phosphatase (ALP) Low        | 9999            | 9999            | 9999            | 9999            |
| Alkaline Phosphatase (ALP) High       | 0               | 0               | 0               | 0               |
| Aspartate Aminotransferase (AST) Low  | 9999            | 9999            | 9999            | 9999            |
| Aspartate Aminotransferase (AST) High | 0               | 0               | 0               | 0               |
| Bilirubin, Direct, Low                | 9999            | 9999            | 9999            | 9999            |
| Bilirubin, Direct, High               | 0               | 0               | 0               | 0               |
| Bilirubin, Total, Low                 | 9999            | 9999            | 9999            | 9999            |
| Bilirubin, Total, High                | 0               | 0               | 2.4             | 0               |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Marked Laboratory Abnormality -- Other Chemistry Testing

|                 |  |
|-----------------|--|
| End point title | Marked Laboratory Abnormality -- Other Chemistry Testing |
|-----------------|--|

End point description:

LIPID TESTS: CHOLESTEROL, TOTAL (TC) CHOL MMOL/L HIGH IF VALUE > 10.36; HDL CHOLESTEROL (HDL-C) HDLC MMOL/L LOW IF VALUE < 1.036; LDL CHOLESTEROL (CALCULATED) FASTING LDLF MMOL/L HIGH IF VALUE >= 4.144; TRIGLYCERIDES, FASTING TRIGF MMOL/L HIGH IF VALUE > 5.65; VLDL CHOLESTEROL (VLDL-C) VLDL MMOL/L HIGH IF VALUE >= 1.294

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

End point timeframe:

From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier

| End point values             | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type           | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed  | 40              | 21              | 42              | 40              |
| Units: Percentage            |                 |                 |                 |                 |
| number (not applicable)      |                 |                 |                 |                 |
| Cholesterol, Total, Low      | 9999            | 9999            | 9999            | 9999            |
| Cholesterol, Total, High     | 0               | 0               | 0               | 0               |
| HDL Cholesterol, Low         | 10.3            | 21.1            | 9.5             | 10.0            |
| HDL, Cholesterol, High       | 9999            | 9999            | 9999            | 9999            |
| LDL Cholesterol (Calc.) Low  | 9999            | 9999            | 9999            | 9999            |
| LDL Cholesterol (Calc.) High | 10.3            | 26.3            | 21.4            | 27.5            |
| Triglycerides, Fasting, Low  | 9999            | 9999            | 9999            | 9999            |
| Triglycerides, Fasting, High | 0               | 0               | 0               | 0               |
| VLDL Cholesterol, Low        | 9999            | 9999            | 9999            | 9999            |
| VLDL Cholesterol, High       | 12.8            | 15.8            | 7.1             | 20.0            |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity -- Percentage of Subjects with ADA Positive Response With Respect to Baseline

|                 |  |
|-----------------|--|
| End point title | Immunogenicity -- Percentage of Subjects with ADA Positive Response With Respect to Baseline |
|-----------------|--|

End point description:

An ADA (anti-drug antibody) positive relative to baseline immunogenicity response using electrochemical luminescence (ECL) assay measurement is defined as: a) A missing baseline immunogenicity measurement and a positive laboratory reported immunogenicity response post-baseline. b) A negative laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline. c) A positive laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline that has a titer value of 9 folds or greater than the baseline titer value. All other ECL immunogenicity measurements will be classified as negative immunogenicity response.

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

End point timeframe:

From the first Clazakizumab dose +1 and up to and including 28 days [represents one dosing interval] after the last dose in the study period

| End point values                                 | PBO + MTX       | C1 + MTX        | C5 + MTX        | C25 + MTX       |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type                               | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                      | 40              | 21              | 42              | 40              |
| Units: Percentage                                |                 |                 |                 |                 |
| number (not applicable)                          |                 |                 |                 |                 |
| ADA +ve At Baseline Visit                        | 0               | 0               | 0               | 2.5             |
| ADA +ve (rel. to bsl.) at only 1 On-Trt Visit    | 0               | 0               | 0               | 0               |
| ADA +ve (rel. to bsl.) at 1 or More On-Trt Visit | 0               | 0               | 0               | 0               |

|   |   |   |   |     |
|---|---|---|---|-----|
| ADA +ve (rel. to bsl.) at 2 or More On-Trt Visits | 0 | 0 | 0 | 0   |
| ADA +ve (rel. to bsl.) at >= 2 Cons. Visits       | 0 | 0 | 0 | 0   |
| ADA +ve (rel. to bsl.) at 1 Post-Trt Visit        | 0 | 0 | 0 | 7.1 |
| ADA +ve (rel. to bsl.) at >=2 Post-Trt Visits     | 0 | 0 | 0 | 0   |
| ADA +ve (rel. to bsl.) at 2 or More Visits        | 0 | 0 | 0 | 0   |

## Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose of study drug in double blind period to 150 days post the last dose if subject discontinued study medication or the first dose date in long term extension period.

Adverse event reporting additional description:

All SAEs were collected during the screening period and within six months of discontinuation of dosing; Collection of non-serious AE information began at initiation of study drug

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matched to clazakizumab subcutaneous (SC) injection once in every four weeks (q4w) for 12 weeks in double-blind period with background of methotrexate.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Clazakizumab 1 mg |
|-----------------------|-------------------|

Reporting group description:

Subjects received 1 milligram (mg) clazakizumab SC injection q4w for 12 weeks in double-blind period and 25 mg clazakizumab SC injection q4w in open-label long term extension period with background of methotrexate.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Clazakizumab 5 mg |
|-----------------------|-------------------|

Reporting group description:

Subjects received 5 mg clazakizumab SC injection q4w for 12 weeks in double-blind period and 25 mg clazakizumab SC injection q4w in open-label long term extension period with background of methotrexate.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Clazakizumab 25 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received 25 mg clazakizumab SC injection q4w in 12 week double-blind period then in open-label long term extension period with background of methotrexate.

| Serious adverse events                               | Placebo        | Clazakizumab 1 mg | Clazakizumab 5 mg |
|--|----------------|-------------------|-------------------|
| Total subjects affected by serious adverse events    |                |                   |                   |
| subjects affected / exposed                          | 2 / 40 (5.00%) | 0 / 21 (0.00%)    | 0 / 42 (0.00%)    |
| number of deaths (all causes)                        | 1              | 0                 | 0                 |
| number of deaths resulting from adverse events       | 1              | 0                 | 0                 |
| General disorders and administration site conditions |                |                   |                   |
| Sudden death   |                |                   |                   |
| subjects affected / exposed                          | 1 / 40 (2.50%) | 0 / 21 (0.00%)    | 0 / 42 (0.00%)    |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all           | 1 / 1          | 0 / 0             | 0 / 0             |
| Gastrointestinal disorders                           |                |                   |                   |
| Abdominal pain                                       |                |                   |                   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 40 (2.50%) | 0 / 21 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 1 / 40 (2.50%) | 0 / 21 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 1 / 40 (2.50%) | 0 / 21 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal impairment                                |                |                |                |
| subjects affected / exposed                     | 1 / 40 (2.50%) | 0 / 21 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 21 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Viral infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 21 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|  |                    |  |  |
|--|--------------------|--|--|
| <b>Serious adverse events</b>                        | Clazakizumab 25 mg |  |  |
| Total subjects affected by serious adverse events    |                    |  |  |
| subjects affected / exposed                          | 2 / 40 (5.00%)     |  |  |
| number of deaths (all causes)                        | 0                  |  |  |
| number of deaths resulting from adverse events       | 0                  |  |  |
| General disorders and administration site conditions |                    |  |  |
| Sudden death   |                    |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 40 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Gastrointestinal disorders</b>               |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 0 / 40 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 0 / 40 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 0 / 40 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Renal and urinary disorders</b>              |                |  |  |
| Renal impairment                                |                |  |  |
| subjects affected / exposed                     | 0 / 40 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Infections and infestations</b>              |                |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 40 (2.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Viral infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 40 (2.50%) |  |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Placebo          | Clazakizumab 1 mg | Clazakizumab 5 mg |
|---|------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events |                  |                   |                   |
| subjects affected / exposed                           | 14 / 40 (35.00%) | 6 / 21 (28.57%)   | 14 / 42 (33.33%)  |
| Investigations  |                  |                   |                   |
| Alanine aminotransferase increased                    |                  |                   |                   |
| subjects affected / exposed                           | 1 / 40 (2.50%)   | 1 / 21 (4.76%)    | 2 / 42 (4.76%)    |
| occurrences (all)                                     | 1                | 1                 | 2                 |
| Gamma-Glutamyltransferase increased                   |                  |                   |                   |
| subjects affected / exposed                           | 1 / 40 (2.50%)   | 0 / 21 (0.00%)    | 1 / 42 (2.38%)    |
| occurrences (all)                                     | 1                | 0                 | 1                 |
| Injury, poisoning and procedural complications        |                  |                   |                   |
| Contusion   |                  |                   |                   |
| subjects affected / exposed                           | 3 / 40 (7.50%)   | 1 / 21 (4.76%)    | 0 / 42 (0.00%)    |
| occurrences (all)                                     | 3                | 1                 | 0                 |
| Nervous system disorders                              |                  |                   |                   |
| Dizziness   |                  |                   |                   |
| subjects affected / exposed                           | 2 / 40 (5.00%)   | 0 / 21 (0.00%)    | 0 / 42 (0.00%)    |
| occurrences (all)                                     | 2                | 0                 | 0                 |
| Headache  |                  |                   |                   |
| subjects affected / exposed                           | 2 / 40 (5.00%)   | 0 / 21 (0.00%)    | 0 / 42 (0.00%)    |
| occurrences (all)                                     | 2                | 0                 | 0                 |
| Blood and lymphatic system disorders                  |                  |                   |                   |
| Leukopenia  |                  |                   |                   |
| subjects affected / exposed                           | 0 / 40 (0.00%)   | 0 / 21 (0.00%)    | 1 / 42 (2.38%)    |
| occurrences (all)                                     | 0                | 0                 | 1                 |
| Neutropenia   |                  |                   |                   |
| subjects affected / exposed                           | 0 / 40 (0.00%)   | 0 / 21 (0.00%)    | 0 / 42 (0.00%)    |
| occurrences (all)                                     | 0                | 0                 | 0                 |
| General disorders and administration site conditions  |                  |                   |                   |
| Injection site erythema                               |                  |                   |                   |
| subjects affected / exposed                           | 0 / 40 (0.00%)   | 0 / 21 (0.00%)    | 1 / 42 (2.38%)    |
| occurrences (all)                                     | 0                | 0                 | 1                 |
| Injection site reaction                               |                  |                   |                   |
| subjects affected / exposed                           | 1 / 40 (2.50%)   | 1 / 21 (4.76%)    | 2 / 42 (4.76%)    |
| occurrences (all)                                     | 1                | 2                 | 2                 |
| Gastrointestinal disorders                            |                  |                   |                   |

|   |   |  |   |
|---|---|--|---|
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 40 (7.50%)<br>3   | 0 / 21 (0.00%)<br>0  | 2 / 42 (4.76%)<br>2   |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 40 (2.50%)<br>1   | 0 / 21 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1   |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Herpes zoster<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Oral herpes<br>subjects affected / exposed<br>occurrences (all)<br><br>Sinusitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 40 (0.00%)<br>0<br><br>1 / 40 (2.50%)<br>1<br><br>3 / 40 (7.50%)<br>3<br><br>2 / 40 (5.00%)<br>2<br><br>2 / 40 (5.00%)<br>2<br><br>2 / 40 (5.00%)<br>3<br><br>1 / 40 (2.50%)<br>1 | 1 / 21 (4.76%)<br>1<br><br>0 / 21 (0.00%)<br>0<br><br>1 / 21 (4.76%)<br>1<br><br>0 / 21 (0.00%)<br>0<br><br>0 / 21 (0.00%)<br>0<br><br>0 / 21 (0.00%)<br>0<br><br>2 / 21 (9.52%)<br>2<br><br>1 / 21 (4.76%)<br>1 | 1 / 42 (2.38%)<br>1<br><br>0 / 42 (0.00%)<br>0<br><br>1 / 42 (2.38%)<br>1<br><br>0 / 42 (0.00%)<br>0<br><br>2 / 42 (4.76%)<br>2<br><br>2 / 42 (4.76%)<br>2<br><br>1 / 42 (2.38%)<br>2 |
| Metabolism and nutrition disorders<br>Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 40 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1   |

|  |                    |  |  |
|--|--------------------|--|--|
| <b>Non-serious adverse events</b>  | Clazakizumab 25 mg |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 15 / 40 (37.50%)   |  |  |

|  |  |  |  |
|--|--|--|--|
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Gamma-Glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)                | 2 / 40 (5.00%)<br>2<br><br>2 / 40 (5.00%)<br>2   |  |  |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all)  | 2 / 40 (5.00%)<br>2                              |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)  | 1 / 40 (2.50%)<br>1<br><br>0 / 40 (0.00%)<br>0   |  |  |
| Blood and lymphatic system disorders<br>Leukopenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)  | 4 / 40 (10.00%)<br>4<br><br>4 / 40 (10.00%)<br>4 |  |  |
| General disorders and administration site conditions<br>Injection site erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site reaction<br>subjects affected / exposed<br>occurrences (all) | 3 / 40 (7.50%)<br>5<br><br>5 / 40 (12.50%)<br>7  |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 40 (0.00%)<br>0                              |  |  |

|   |   |  |  |
|---|---|--|--|
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 40 (2.50%)<br>1   |  |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Herpes zoster<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Oral herpes<br>subjects affected / exposed<br>occurrences (all)<br><br>Sinusitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 40 (5.00%)<br>2<br><br>2 / 40 (5.00%)<br>3<br><br>2 / 40 (5.00%)<br>3<br><br>0 / 40 (0.00%)<br>0<br><br>1 / 40 (2.50%)<br>1<br><br>2 / 40 (5.00%)<br>2<br><br>1 / 40 (2.50%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 40 (5.00%)<br>2   |  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported