



Clinical trial results:

An Open-label Extension Study to Evaluate the Long-term Safety of Mavrilimumab in Adult Participants with Rheumatoid Arthritis

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2011-005648-93 |
| Trial protocol | EE HU CZ DE ES BG GR SK PT GB |
| Global end of trial date | 30 September 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 March 2017 |
| First version publication date | 15 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------------------|
| Sponsor protocol code | CD-IA-CAM-3001-1109 |
|-----------------------|---------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01712399 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | MedImmune, LLC. |
| Sponsor organisation address | Milstein Building, Granta Park, Cambridge, CB21 6GH, United Kingdom, |
| Public contact | Marius Albulescu, MD, MedImmune, LLC., +44 (0) 301-398-0000, clinicaltrialsenquiries@medimmune.com |
| Scientific contact | Marius Albulescu, MD, MedImmune, LLC., +44 (0) 301-398-0000, clinicaltrialsenquiries@medimmune.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 | 30 September 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 September 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term safety of mavrilimumab in adult participants with moderate-to-severe active Rheumatoid Arthritis (RA) who were previously treated in a qualifying study.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Participating participant signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 February 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Bulgaria: 3 |
| Country: Number of subjects enrolled | Argentina: 41 |
| Country: Number of subjects enrolled | Chile: 35 |
| Country: Number of subjects enrolled | Colombia: 25 |
| Country: Number of subjects enrolled | Czech Republic: 69 |
| Country: Number of subjects enrolled | Estonia: 21 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Hungary: 9 |
| Country: Number of subjects enrolled | Israel: 11 |
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | Poland: 34 |
| Country: Number of subjects enrolled | Russian Federation: 53 |
| Country: Number of subjects enrolled | Serbia: 24 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Country: Number of subjects enrolled | Spain: 4 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Ukraine: 39 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Worldwide total number of subjects | 397 |
| EEA total number of subjects | 157 |

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) | 354 |
| From 65 to 84 years | 43 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 409 participants consented and 397 participants received mavrilimumab in this study.

Pre-assignment

Screening details:

A total of 442 participants who received at least one dose of mavrilimumab provided a pooled analysis of safety and efficacy data from this open-label extension study (CD IA CAM 3001 1109) together with the qualifying studies (CD IA CAM 3001 1071 and CD IA CAM 3001 1107).

Period 1

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

Arms

| | |
|------------------|---------------------|
| Arm title | Mavrilimumab 100 mg |
|------------------|---------------------|

Arm description:

Participants received 100 mg mavrilimumab once in every 2 weeks (Q2W) subcutaneously for up to 3 years.

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

Dosage and administration details:

Participants received 100 mg mavrilimumab once in every 2 weeks (Q2W) subcutaneously for up to 3 years.

| | |
|---------------------------------------|---------------------|
| Number of subjects in period 1 | Mavrilimumab 100 mg |
| Started | 397 |
| Completed | 0 |
| Not completed | 397 |
| Adverse event, serious fatal | 1 |
| Consent withdrawn by subject | 39 |
| Adverse event, non-fatal | 11 |
| Lost to follow-up | 1 |
| Study closure | 345 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Mavrilimumab 100 mg |
|-----------------------|---------------------|

Reporting group description:

Participants received 100 mg mavrilimumab once in every 2 weeks (Q2W) subcutaneously for up to 3 years.

| Reporting group values | Mavrilimumab 100 mg | Total | |
|--|---------------------|-------|--|
| Number of subjects | 397 | 397 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 354 | 354 | |
| From 65-84 years | 43 | 43 | |
| 85 years and over | 0 | 0 | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 51.1 | | |
| standard deviation | ± 11.2 | - | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 339 | 339 | |
| Male | 58 | 58 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaskan Native | 29 | 29 | |
| Asian | 1 | 1 | |
| Black or African American | 1 | 1 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| White | 364 | 364 | |
| Other | 2 | 2 | |
| Region of Enrollment Units: Subjects | | | |
| ARGENTINA | 41 | 41 | |
| BULGARIA | 3 | 3 | |
| CHILE | 35 | 35 | |
| COLOMBIA | 25 | 25 | |
| CZECH REPUBLIC | 69 | 69 | |
| ESTONIA | 21 | 21 | |
| GERMANY | 8 | 8 | |
| GREECE | 3 | 3 | |

| | | | |
|--|--------|----|--|
| HUNGARY | 9 | 9 | |
| ISRAEL | 11 | 11 | |
| MEXICO | 10 | 10 | |
| POLAND | 34 | 34 | |
| RUSSIAN FEDERATION | 53 | 53 | |
| SERBIA | 24 | 24 | |
| SLOVAKIA | 1 | 1 | |
| SOUTH AFRICA | 2 | 2 | |
| SPAIN | 4 | 4 | |
| UKRAINE | 39 | 39 | |
| UNITED KINGDOM | 5 | 5 | |
| Study Specific Characteristic Weight | | | |
| Units: Kilogram | | | |
| arithmetic mean | 73.25 | | |
| standard deviation | ± 16.4 | - | |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | Mavrilimumab 100 mg |
| Reporting group description: | |
| Participants received 100 mg mavrilimumab once in every 2 weeks (Q2W) subcutaneously for up to 3 years. | |

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

| | |
|-----------------|---|
| End point title | Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) ^[1] |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence attributed to study drug in a participant who received investigational product. A serious adverse event (SAE) was an AE resulting in any of following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs were defined as AEs with onset date after the first dose of mavrilimumab 100 mg. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of study drug administration up to 12 weeks after the last dose of study drug (approximately up to 3 years)

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| | | | | |
|-----------------------------|---------------------|--|--|--|
| End point values | Mavrilimumab 100 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | | | | |
| TEAEs | 288 | | | |
| TESAEs | 46 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinical Laboratory Abnormalities Reported as Treatment-Emergent Adverse Events (TEAEs)

| | |
|-----------------|--|
| End point title | Number of Participants With Clinical Laboratory Abnormalities Reported as Treatment-Emergent Adverse Events (TEAEs) ^[2] |
|-----------------|--|

End point description:

Laboratory parameters included hematology, serum chemistry and urinalysis recorded as TEAEs. Clinical laboratory abnormalities recorded as TEAEs were reported. TEAEs were defined as AEs with onset date after the first dose of mavrilimumab 100 mg. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of study drug administration in the study up to 12 weeks after the last dose of study drug (approximately up to 3 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Mavrilimumab 100 mg | | | |
|---|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | | | | |
| Anaemia | 8 | | | |
| Eosinophilia | 1 | | | |
| Iron deficiency anaemia | 2 | | | |
| Leukocytosis | 1 | | | |
| Leukopenia | 1 | | | |
| Lymphadenopathy | 1 | | | |
| Neutropenia | 2 | | | |
| Spontaneous haematoma | 1 | | | |
| Alanine aminotransferase increased | 8 | | | |
| Aspartate aminotransferase increased | 6 | | | |
| Blood creatinine increased | 1 | | | |
| Blood glucose increased | 1 | | | |
| Blood pressure increased | 3 | | | |
| C-reactive protein increased | 1 | | | |
| Chest X-ray abnormal | 1 | | | |
| Forced vital capacity abnormal | 1 | | | |
| Gamma-glutamyltransferase increased | 2 | | | |
| Hepatic enzyme increased | 2 | | | |
| Liver function test abnormal | 1 | | | |
| Mycobacterium tuberculosis complex test positive | 1 | | | |
| Neutrophil count decreased | 1 | | | |
| Red blood cell sedimentation rate increased | 1 | | | |
| Transaminases increased | 3 | | | |
| Diabetes mellitus | 5 | | | |
| Dyslipidaemia | 4 | | | |
| Hypercholesterolaemia | 9 | | | |
| Hyperglycaemia | 3 | | | |
| Hyperlipidaemia | 2 | | | |
| Hypertriglyceridaemia | 2 | | | |
| Hypoglycaemia | 1 | | | |
| Type 2 diabetes mellitus | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Vital Sign Abnormalities Reported as Treatment-Emergent Adverse Events (TEAEs)

| | |
|-----------------|---|
| End point title | Number of Participants With Vital Sign Abnormalities Reported as Treatment-Emergent Adverse Events (TEAEs) ^[3] |
|-----------------|---|

End point description:

Vital sign assessments included blood pressure, pulse rate, temperature, weight, and respiration rate. Vital sign abnormalities recorded as TEAEs were reported. TEAEs were defined as AEs with onset date after the first dose of mavrilimumab 100 mg. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of study drug administration in the study up to 12 weeks after the last dose of study drug (approximately up to 3 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| | | | | |
|-----------------------------|---------------------|--|--|--|
| End point values | Mavrilimumab 100 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | | | | |
| Hypertension | 26 | | | |
| Pyrexia | 3 | | | |
| Blood pressure increased | 3 | | | |
| Atrial fibrillation | 1 | | | |
| Palpitations | 1 | | | |
| Sinus tachycardia | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Electrocardiogram (ECG) Findings Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Participants With Abnormal Electrocardiogram (ECG) Findings Reported as TEAEs ^[4] |
|-----------------|--|

End point description:

The 12-lead ECG data were summarized and evaluated. TEAEs related to abnormal ECG findings were recorded and reported. TEAEs were defined as AEs with onset date after the first dose of mavrilimumab 100 mg. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of study drug administration in the study up to 12 weeks after the last dose of study drug (approximately up to 3 years)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Mavrilimumab 100 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Forced Expiratory Volume in 1 Second (FEV1) Outside Threshold Values

| | |
|-----------------|---|
| End point title | Number of Participants With Forced Expiratory Volume in 1 Second (FEV1) Outside Threshold Values ^[5] |
|-----------------|---|

End point description:

Pulmonary function testing was performed by spirometry to assess forced expiratory volume in 1 second (FEV1). FEV1 was the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. The percentage (%) of predicted values of these pulmonary function tests were calculated based on decrease from baseline and categorized as less than or equal to (\leq) 15% reduction from baseline, greater than ($>$) 15% to \leq 20% reduction from baseline, $>$ 20% reduction from baseline and $>$ 20% reduction to $<$ 80%. The threshold values refer to baseline values for each participant. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W. Here 'n' represents those participants who were evaluable for this measure at given time points.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Week 24 to Week 130 at specified time points

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| | | | | |
|--|------------------------|--|--|--|
| End point values | Mavrilimumab 100 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | | | | |
| Week 24 (n=236): \leq 15% reduction | 208 | | | |
| Week 24 (n=236): $>$ 15% to \leq 20% | 12 | | | |
| Week 24 (n=236): $>$ 20% reduction | 16 | | | |
| Week 24 (n=236): $>$ 20% to $<$ 80% | 13 | | | |
| Week 48 (n=231): \leq 15% reduction | 208 | | | |
| Week 48 (n=231): $>$ 15% to \leq 20% | 10 | | | |
| Week 48 (n=231): $>$ 20% reduction | 13 | | | |
| Week 48 (n=231): $>$ 20% to $<$ 80% | 8 | | | |
| Week 78 (n=178): \leq 15% reduction | 154 | | | |
| Week 78 (n=178): $>$ 15% to \leq 20% | 8 | | | |
| Week 78 (n=178): $>$ 20% reduction | 16 | | | |
| Week 78 (n=178): $>$ 20% to $<$ 80% | 11 | | | |
| Week 104 (n=29): \leq 15% reduction | 28 | | | |
| Week 104 (n=29): $>$ 15% to \leq 20% | 0 | | | |
| Week 104 (n=29): $>$ 20% reduction | 1 | | | |
| Week 104 (n=29): $>$ 20% to $<$ 80% | 1 | | | |

| | | | | |
|--------------------------------|---|--|--|--|
| Week 130 (n=3):=<15% reduction | 3 | | | |
| Week 130 (n=3):>15% to =<20% | 0 | | | |
| Week 130 (n=3):>20% reduction | 0 | | | |
| Week 130 (n=3):>20% to <80% | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Forced Expiratory Volume in 6 Seconds (FEV6) Outside Threshold Values

| | |
|-----------------|--|
| End point title | Number of Participants With Forced Expiratory Volume in 6 Seconds (FEV6) Outside Threshold Values ^[6] |
|-----------------|--|

End point description:

Pulmonary function testing was performed by spirometry to assess forced expiratory volume in 6 seconds (FEV6). FEV6 was the maximal volume of air exhaled in the six second of a forced expiration from a position of full inspiration. The percentage of predicted values of these pulmonary function tests were calculated based on decrease from baseline and categorized as =<15% reduction from baseline, >15% to =<20% reduction from baseline, >20% reduction from baseline and >20% reduction to <80%. The threshold values refer to baseline values for each participant. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W. Here 'n' represents those participants who were evaluable for this measure at given time points.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Week 24 to Week 130 at specified time points

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Mavrilimumab 100 mg | | | |
|---------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | | | | |
| Week 24 (n=222):=<15% reduction | 195 | | | |
| Week 24 (n=222):>15% to =<20% | 14 | | | |
| Week 24 (n=222):>20% reduction | 13 | | | |
| Week 24 (n=222):>20% to <80% | 9 | | | |
| Week 48 (n=222):=<15% reduction | 201 | | | |
| Week 48 (n=222):>15% to =<20% | 13 | | | |
| Week 48 (n=222):>20% reduction | 8 | | | |
| Week 48 (n=222):>20% to <80% | 4 | | | |
| Week 78 (n=172):=<15% reduction | 150 | | | |
| Week 78 (n=172):>15% to =<20% | 8 | | | |
| Week 78 (n=172):>20% reduction | 14 | | | |
| Week 78 (n=172):>20% to <80% | 5 | | | |
| Week 104 (n=28):=<15% reduction | 27 | | | |
| Week 104 (n=28):>15% to =<20% | 0 | | | |
| Week 104 (n=28):>20% reduction | 1 | | | |
| Week 104 (n=28):>20% to <80% | 1 | | | |
| Week 130 (n=3):=<15% reduction | 1 | | | |

| | | | | |
|-------------------------------|---|--|--|--|
| Week 130 (n=3):>15% to =<20% | 0 | | | |
| Week 130 (n=3):>20% reduction | 2 | | | |
| Week 130 (n=3):>20% to <80% | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Forced Vital Capacity (FVC) Outside Threshold Values

| | |
|-----------------|---|
| End point title | Number of Participants With Forced Vital Capacity (FVC) Outside Threshold Values ^[7] |
|-----------------|---|

End point description:

Pulmonary function testing was performed by spirometry to assess forced vital capacity (FVC). FVC was the volume of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. The percentage of predicted values of these pulmonary function tests were calculated based on decrease from baseline and categorized as =<15% reduction from baseline, >15% to =<20% reduction from baseline, >20% reduction from baseline and >20% reduction to <80%. The threshold values refer to baseline values for each participant. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W. Here 'n' represents those participants who were evaluable for this measure at given time points.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Week 24 to Week 156 at specified time points

Notes:

[7] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Mavrilimumab 100 mg | | | |
|---------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Participants | | | | |
| Week 24 (n=233):=<15% reduction | 209 | | | |
| Week 24 (n=233):>15% to =<20% | 13 | | | |
| Week 24 (n=233):>20% reduction | 11 | | | |
| Week 24 (n=233):>20% to <80% | 7 | | | |
| Week 48 (n=239):=<15% reduction | 218 | | | |
| Week 48 (n=239):>15% to =<20% | 10 | | | |
| Week 48 (n=239):>20% reduction | 11 | | | |
| Week 48 (n=239):>20% to <80% | 7 | | | |
| Week 78 (n=177):=<15% reduction | 160 | | | |
| Week 78 (n=177):>15% to =<20% | 4 | | | |
| Week 78 (n=177):>20% reduction | 13 | | | |
| Week 78 (n=177):>20% to <80% | 6 | | | |
| Week 104 (n=32):=<15% reduction | 32 | | | |
| Week 104 (n=32):>15% to =<20% | 0 | | | |
| Week 104 (n=32):>20% reduction | 0 | | | |
| Week 104 (n=32):>20% to <80% | 0 | | | |
| Week 130 (n=5):=<15% reduction | 4 | | | |
| Week 130 (n=5):>15% to =<20% | 0 | | | |

| | | | | |
|--------------------------------|---|--|--|--|
| Week 130 (n=5):>20% reduction | 1 | | | |
| Week 130 (n=5):>20% to <80% | 1 | | | |
| Week 156 (n=2):=<15% reduction | 2 | | | |
| Week 156 (n=2):>15% to =<20% | 0 | | | |
| Week 156 (n=2):>20% reduction | 0 | | | |
| Week 156 (n=2):>20% to <80% | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Meaningful Change in Borg Dyspnea Score Considered as an AE

| | |
|-----------------|---|
| End point title | Number of Participants With Clinically Meaningful Change in Borg Dyspnea Score Considered as an AE ^[8] |
|-----------------|---|

End point description:

Borg dyspnea score was a validated participant reported outcome assessing participant's perceived difficulty in breathing (dyspnea). The score ranges from 0 (nothing at all) to 10 (maximal difficulty). Higher scores indicated greater difficulty in breathing. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Week 0 to Week 132 at specified time points

Notes:

[8] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| | | | | |
|-----------------------------|---------------------|--|--|--|
| End point values | Mavrilimumab 100 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 394 | | | |
| Units: Participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Oxygen Saturation Levels by Pulse Oximetry

| | |
|-----------------|---|
| End point title | Oxygen Saturation Levels by Pulse Oximetry ^[9] |
|-----------------|---|

End point description:

Oxygen saturation measured by pulse oximetry which measures the concentration of oxygen in the blood. 99999 indicates non-availability of data as standard error was not calculated due to limited sample size. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W. Here 'n' represents those participants who were evaluable for this measure at given time points.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Week 0 to Week 132 at specified time points

Notes:

[9] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Mavrilimumab 100 mg | | | |
|----------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: Percent saturation | | | | |
| arithmetic mean (standard error) | | | | |
| Week 0 (n=397) | 97.6 (± 0.1) | | | |
| Week 12 (n=384) | 97.6 (± 0.1) | | | |
| Week 24 (n=1) | 98 (± 99999) | | | |
| Week 36 (n=357) | 97.5 (± 0.1) | | | |
| Week 48 (n=327) | 97.8 (± 0.1) | | | |
| Week 60 (n=281) | 97.8 (± 0.1) | | | |
| Week 72 (n=233) | 97.7 (± 0.1) | | | |
| Week 84 (n=222) | 97.7 (± 0.1) | | | |
| Week 96 (n=188) | 97.9 (± 0.1) | | | |
| Week 108 (n=58) | 97.8 (± 0.2) | | | |
| Week 120 (n=18) | 97.6 (± 0.3) | | | |
| Week 132 (n=7) | 97.9 (± 0.5) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Diffusing Capacity of the Lung for Carbon Monoxide (DLCO)

| | |
|-----------------|---|
| End point title | Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) ^[10] |
|-----------------|---|

End point description:

DLCO is a pulmonary function testing that measures partial pressure difference between inspired and expired carbon monoxide. The unit mL/min/mmHg refers to milliliter/minute/millimeter of mercury. The As-treated Population included participants who received at least one dose of mavrilimumab 100 mg Q2W. Here 'n' represents those participants who were evaluable for this measure at given time points.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Week 12 to Week 156 at specified time points

Notes:

[10] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Mavrilimumab 100 mg | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 397 | | | |
| Units: mL/min/mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 (n=80) | 21.196 (± 5.158) | | | |

| | | | | |
|------------------|------------------|--|--|--|
| Week 24 (n=155) | 21.996 (± 5.274) | | | |
| Week 48 (n=203) | 21.135 (± 4.873) | | | |
| Week 78 (n=165) | 20.639 (± 4.637) | | | |
| Week 104 (n=144) | 20.636 (± 5.088) | | | |
| Week 130 (n=52) | 20.372 (± 4.546) | | | |
| Week 156 (n=6) | 19.265 (± 4.131) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study drug administration up to 12 weeks after the last dose of study drug (approximately up to 3 years)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Mavrilimumab 100 mg |
|-----------------------|---------------------|

Reporting group description:

Participants received 100 mg mavrilimumab once in every 2 weeks (Q2W) subcutaneously for up to 3 years.

| Serious adverse events | Mavrilimumab 100 mg | | |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 46 / 397 (11.59%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer female | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyogenic granuloma | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 2 / 397 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |

| | | | |
|--|-----------------|--|--|
| Peripheral arterial occlusive disease subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery stenosis subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery thrombosis subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subclavian artery thrombosis subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiopulmonary failure subjects affected / exposed | 2 / 397 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction subjects affected / exposed | 2 / 397 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Myelitis transverse subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 397 (0.76%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Foot deformity | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 397 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 4 / 397 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendiceal abscess | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 4 / 397 (1.01%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 2 / 397 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary tuberculosis | | | | |
| subjects affected / exposed | 2 / 397 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyomyositis | | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sialoadenitis | | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 397 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Mavrilimumab 100 mg | | |
|---|---------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 214 / 397 (53.90%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 8 / 397 (2.02%) | | |
| occurrences (all) | 8 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 8 / 397 (2.02%) | | |
| occurrences (all) | 8 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 26 / 397 (6.55%) | | |
| occurrences (all) | 27 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 397 (4.28%) | | |
| occurrences (all) | 35 | | |
| Gastrointestinal disorders | | | |
| Dental caries | | | |
| subjects affected / exposed | 8 / 397 (2.02%) | | |
| occurrences (all) | 9 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 397 (3.78%) | | |
| occurrences (all) | 15 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 397 (2.02%) | | |
| occurrences (all) | 9 | | |

| | | | |
|---|-------------------|--|--|
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 12 / 397 (3.02%) | | |
| occurrences (all) | 13 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 12 / 397 (3.02%) | | |
| occurrences (all) | 13 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 38 / 397 (9.57%) | | |
| occurrences (all) | 78 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 44 / 397 (11.08%) | | |
| occurrences (all) | 59 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 11 / 397 (2.77%) | | |
| occurrences (all) | 14 | | |
| Influenza | | | |
| subjects affected / exposed | 23 / 397 (5.79%) | | |
| occurrences (all) | 26 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 59 / 397 (14.86%) | | |
| occurrences (all) | 90 | | |
| Oral herpes | | | |
| subjects affected / exposed | 11 / 397 (2.77%) | | |
| occurrences (all) | 13 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 18 / 397 (4.53%) | | |
| occurrences (all) | 20 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 13 / 397 (3.27%) | | |
| occurrences (all) | 21 | | |
| Rhinitis | | | |
| subjects affected / exposed | 9 / 397 (2.27%) | | |
| occurrences (all) | 10 | | |
| Upper respiratory tract infection | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 31 / 397 (7.81%) | | |
| occurrences (all) | 43 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 35 / 397 (8.82%) | | |
| occurrences (all) | 53 | | |
| Viral infection | | | |
| subjects affected / exposed | 8 / 397 (2.02%) | | |
| occurrences (all) | 10 | | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 9 / 397 (2.27%) | | |
| occurrences (all) | 9 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 18 December 2012 | Reference to the Data safety monitoring board (DSMB) was removed from the Study-stopping Criteria, Definition of the timing of the withdrawal visit was added, Withdrawal criteria item revised to include a definition of inadequate response, A section describing unblinding in the event of a suspected unexpected serious adverse reaction (SUSAR) was added, Responsibilities for the decision to resume administration of investigational product for a participant referred for a specialist pulmonary evaluation were clarified, A DLCO assessment was added, Reference to recording the QT interval during the electrocardiogram (ECG) was removed, Text describing an additional serum sample collection was added, The estimate of volume of blood to be collected was amended and Mention of flow cytometry was deleted from the exploratory endpoints and the protocol abstract |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-------------------|---|--------------|
| 30 September 2015 | The study was terminated after approximately 3 years due to future clinical development plans, including ethical considerations (the 100 mg Q2W dose was considered suboptimal compared with 150 mg Q2W based on CD-IA-CAM-3001-1071 data). | - |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated after approximately 3 years due to future clinical development plans, including ethical considerations (the 100 mg Q2W dose was considered suboptimal compared with 150 mg Q2W based on CD-IA-CAM-3001-1071 data).

Notes: