



Clinical trial results:

A Multicenter, Single-blind, Randomized Parallel-group Study to Assess the Short- and Long-term Efficacy of Certolizumab Pegol Plus Methotrexate Compared with Adalimumab Plus Methotrexate in Subjects With Moderate To Severe Rheumatoid Arthritis Responding Inadequately to Methotrexate

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2011-002067-20 |
| Trial protocol | DE GB HU PT AT IE CZ ES BG FR IT GR |
| Global end of trial date | 13 January 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 27 April 2017 |
| First version publication date | 09 December 2016 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | RA0077 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01500278 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Pharma SA |
| Sponsor organisation address | Allée de la Recherche 60, Brussels, Belgium, B-1070 |
| Public contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |
| Scientific contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.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 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate the superiority of short-term (Week 12) treatment in Certolizumab pegol (CZP)+Methotrexate (MTX)-randomized subjects as compared with Adalimumab (ADA)+MTX-randomized subjects
- To demonstrate the superiority of long-term (Week 104) treatment in CZP+MTX-randomized subjects as compared with ADA+MTX-randomized subjects, with subjects who switch treatment (Week 12 Non-Responders) counted as treatment failures

Protection of trial subjects:

Not applicable.

Background therapy:

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. The same dosing regimen (dose and route) was maintained from Baseline through Week 52. At Week 52, subjects were allowed to switch regimens (dose and/or route), but had to continue with an MTX dose of 15 to 25mg/week through Week 104 and were not allowed to change the MTX regimen after Week 52. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously. All subjects were responsible for providing their own MTX, consistent with their provision for such at entry.

Other background therapy as permitted in the protocol.

Evidence for comparator:

Adalimumab is a well established anti-TNF.

| | |
|---|------------------|
| Actual start date of recruitment | 14 December 2011 |
| 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 | Australia: 27 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Bulgaria: 78 |
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | Czech Republic: 118 |
| Country: Number of subjects enrolled | France: 25 |
| Country: Number of subjects enrolled | Germany: 62 |
| Country: Number of subjects enrolled | Hungary: 58 |
| Country: Number of subjects enrolled | Ireland: 5 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Mexico: 38 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 130 |
| Country: Number of subjects enrolled | Portugal: 13 |
| Country: Number of subjects enrolled | Romania: 52 |
| Country: Number of subjects enrolled | Spain: 34 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | United States: 226 |
| Worldwide total number of subjects | 915 |
| EEA total number of subjects | 603 |

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) | 737 |
| From 65 to 84 years | 178 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in December 2011 and concluded in January 2016.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Treatment Group (RTG) that consisted of all subjects randomized into the study.

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Week 0 - Week 12 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | CZP+MTX (RTG) |

Arm description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.

Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

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

Dosage and administration details:

CZP+MTX group: Subcutaneous injections of CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 Responders.

ADA+MTX group: Subcutaneous injections of CZP 400 mg at Week 12, 14 and 16 followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 ADA+MTX Non-Responders.

| | |
|------------------|---------------|
| Arm title | ADA+MTX (RTG) |
|------------------|---------------|

Arm description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.

Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--|
| Investigational medicinal product name | Adalimumab |
| Investigational medicinal product code | ADA |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

ADA+MTX group: Subcutaneous injections of ADA 40mg at Baseline and then every 2 weeks through Week 102 for Week 12 Responders.

CZP+MTX group: Subcutaneous injections of ADA 40mg at Week 12 and every 2 weeks through Week 102 for Week 12 CZP+MTX Non-Responders.

| | |
|--|--|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PBO |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects in group ADA+MTX received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.

| Number of subjects in period 1 | CZP+MTX (RTG) | ADA+MTX (RTG) |
|---------------------------------------|----------------------|----------------------|
| Started | 457 | 458 |
| Completed | 426 | 428 |
| Not completed | 31 | 30 |
| Prior history of serious disease | 1 | - |
| Exclusion criteria not met | 1 | - |
| Adverse event (AE), not fatal | 7 | 8 |
| Sponsor decision | 1 | - |
| Consent withdrawn by subject | 7 | 2 |
| Patient decision | 1 | - |
| Personal reason | - | 1 |
| Investigator decision | 1 | - |
| Protocol violation on screening X-ray | 1 | - |
| Other serious disease | - | 1 |
| Lost to follow-up | 1 | 1 |
| Protocol deviation | 10 | 16 |
| Lack of efficacy | - | 1 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Week 13 - Week 104 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Investigator ^[1] |

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | CZP+MTX (RTG) |

Arm description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.

Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

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

Dosage and administration details:

ADA+MTX group: Subcutaneous injections of ADA 40mg at Baseline and then every 2 weeks through Week 102 for Week 12 Responders.

CZP+MTX group: Subcutaneous injections of ADA 40mg at Week 12 and every 2 weeks through Week 102 for Week 12 CZP+MTX Non-Responders.

| | |
|--|--|
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CZP |
| Other name | Cimzia |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

CZP+MTX group: Subcutaneous injections of CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 Responders.

ADA+MTX group: Subcutaneous injections of CZP 400 mg at Week 12, 14 and 16 followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 ADA+MTX Non-Responders.

| | |
|------------------|---------------|
| Arm title | ADA+MTX (RTG) |
|------------------|---------------|

Arm description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.

Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--|
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CZP |
| Other name | Cimzia |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

CZP+MTX group: Subcutaneous injections of CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 Responders.

ADA+MTX group: Subcutaneous injections of CZP 400 mg at Week 12, 14 and 16 followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 ADA+MTX Non-Responders.

| | |
|--|--|
| Investigational medicinal product name | Adalimumab |
| Investigational medicinal product code | ADA |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

ADA+MTX group: Subcutaneous injections of ADA 40mg at Baseline and then every 2 weeks through Week 102 for Week 12 Responders.

CZP+MTX group: Subcutaneous injections of ADA 40mg at Week 12 and every 2 weeks through Week 102 for Week 12 CZP+MTX Non-Responders.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Period 2 of the study (Week 13 – Week 104) was single blinded, as only investigators were blinded, subjects were not.

| Number of subjects in period 2 | CZP+MTX (RTG) | ADA+MTX (RTG) |
|---|----------------------|----------------------|
| Started | 426 | 428 |
| Completed | 287 | 302 |
| Not completed | 139 | 126 |
| Adverse event, serious fatal | 2 | 4 |
| Relocation | - | 1 |
| Exclusion criteria not met | 1 | - |
| Patient declined Safety Follow Up Visit | 1 | - |
| Abnormal questionable chest X-ray | - | 2 |
| Medical monitor decision | - | 2 |
| Non/bad compliance | 7 | 5 |
| Sponsor decision | - | 2 |
| Recurrent infections | 1 | - |
| Consent withdrawn by subject | 22 | 13 |
| Withdrawn in error | 1 | - |
| Protocol violation | 1 | - |
| Adverse event, non-fatal | 54 | 54 |
| Personal reason | - | 1 |
| False positive test | 1 | 2 |
| Sponsor request | 4 | - |
| Week 24 Non-Responder | 20 | 16 |

| | | |
|---------------------------------|----|----|
| Lost to follow-up | 6 | 5 |
| Principal investigator retiring | 1 | - |
| Lack of efficacy | 11 | 12 |
| Protocol deviation | 6 | 6 |
| Not completed | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | CZP+MTX (RTG) |
|-----------------------|---------------|

Reporting group description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.

Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| | |
|-----------------------|---------------|
| Reporting group title | ADA+MTX (RTG) |
|-----------------------|---------------|

Reporting group description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.

Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| Reporting group values | CZP+MTX (RTG) | ADA+MTX (RTG) | Total |
|-------------------------|---------------|---------------|-------|
| Number of subjects | 457 | 458 | 915 |
| Age Categorical | | | |
| Units: Subjects | | | |
| <=18 years | 0 | 1 | 1 |
| Between 18 and 65 years | 364 | 372 | 736 |
| >=65 years | 93 | 85 | 178 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.5 | 52.9 | |
| standard deviation | ± 12.3 | ± 12.8 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 360 | 363 | 723 |
| Male | 97 | 95 | 192 |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | CZP+MTX (RTG) |
| Reporting group description: | |
| Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10. | |
| Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102. | |
| Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued ADA treatment and were withdrawn from the Treatment Period. | |
| All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously. | |
| Reporting group title | ADA+MTX (RTG) |
| Reporting group description: | |
| Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4. | |
| Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102. | |
| Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued CZP treatment and were withdrawn from the Treatment Period. | |
| All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously. | |
| Reporting group title | CZP+MTX (RTG) |
| Reporting group description: | |
| Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10. | |
| Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102. | |
| Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued ADA treatment and were withdrawn from the Treatment Period. | |
| All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously. | |
| Reporting group title | ADA+MTX (RTG) |
| Reporting group description: | |
| Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4. | |
| Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102. | |
| Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued CZP treatment and were withdrawn from the Treatment Period. | |
| All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously. | |
| Subject analysis set title | CZP+MTX (SS) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All subjects who received at least 1 dose of Certolizumab pegol (CZP). | |
| All adverse events that occurred when the subject was receiving CZP treatment are summarized in this group. | |
| Subject analysis set title | ADA+MTX (SS) |

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All subjects who received at least 1 dose of Adalimumab (ADA).

All adverse events that occurred when the subject was receiving ADA treatment are summarized in this group.

| | |
|----------------------------|---------------|
| Subject analysis set title | CZP+MTX (FAS) |
|----------------------------|---------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.

Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| | |
|----------------------------|---------------|
| Subject analysis set title | ADA+MTX (FAS) |
|----------------------------|---------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.

Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.

Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥ 1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | CZP+MTX (Week 12 Responder Set) |
|----------------------------|---------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until Week 102.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | ADA+MTX (Week 12 Responder Set) |
|----------------------------|---------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

ADA 40 mg at Baseline and then every 2 Weeks until Week 102. Subjects received PBO in addition to ADA at baseline and weeks 2 and 4 in order to maintain the blinding.

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Primary: Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 12

| | |
|-----------------|--|
| End point title | Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 12 |
|-----------------|--|

End point description:

Subjects who met the ACR20 criteria were those subjects with at least 20% improvement from Baseline for Tender Joint Count (TJC), Swollen Joint Count (SJC), and at least 3 of the 5 remaining core set measures: 1) Health Assessment Questionnaire-Disability Index (HAQ-DI), 2) C-reactive Protein (CRP), 3) Patient's Assessment of Arthritis Pain-Visual Analog Scale (PAAP-VAS), 4) Patient's Global Assessment of Disease Activity-Visual Analog Scale (PtGADA-VAS), 5) Physician's Global Assessment of Disease Activity-Visual Analog Scale (PhGA-VAS).

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

End point timeframe:

Week 12

| End point values | CZP+MTX (FAS) | ADA+MTX (FAS) | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 454 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 69.2 | 71.4 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Odds Ratio for Difference in Responders |
| Comparison groups | CZP+MTX (FAS) v ADA+MTX (FAS) |
| Number of subjects included in analysis | 908 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.467 ^[1] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.2 |

Notes:

[1] - The odds ratio, CI, and p-value are from a logistic regression model with RTG, gender, Baseline duration of RA (<2 years or >=2 years), and geographic region as factors and age as a covariate.

Primary: Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104

| | |
|-----------------|---|
| End point title | Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104 |
|-----------------|---|

End point description:

DAS28 [ESR] was calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC), Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula: $0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \times \log_{10}(ESR) + 0.014 \times \text{Patient Global Assessment of Arthritis}$, where 28 joints were examined and a lower score indicates less disease activity.

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

End point timeframe:

Week 104

| End point values | CZP+MTX (FAS) | ADA+MTX (FAS) | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 454 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 35.5 | 33.5 | | |

Statistical analyses

| Statistical analysis title | Odds Ratio for Difference in Responders |
|---|---|
| Comparison groups | CZP+MTX (FAS) v ADA+MTX (FAS) |
| Number of subjects included in analysis | 908 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.532 ^[2] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.45 |

Notes:

[2] - The odds ratio, CI and p-value are from a logistic regression model with RTG, gender, Baseline duration of RA (<2 years or ≥2 years), and geographic region as factors and Baseline DAS28(ESR) and age as covariates.

Secondary: Percentage of Week 12 responders who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104

| | |
|-----------------|---|
| End point title | Percentage of Week 12 responders who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104 |
|-----------------|---|

End point description:

DAS28 [ESR] was calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC), Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula: $0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \times \log_{10}(ESR) + 0.014 \times \text{Patient Global Assessment of Arthritis}$, where 28 joints were examined and a lower score indicates less disease activity.

The definition of Week 12 responders was DAS28[ESR] Low Disease Activity (LDA) (ie ≤ 3.2) or an improvement of ≥ 1.2 in DAS28[ESR] relative to Baseline.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 104 | |

| End point values | CZP+MTX (Week 12 Responder Set) | ADA+MTX (Week 12 Responder Set) | | |
|-------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 353 | 361 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 45.6 | 42.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 6

| | |
|-----------------|---|
| End point title | Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 6 |
|-----------------|---|

End point description:

Subjects who met the ACR20 criteria were those subjects with at least 20% improvement from Baseline for Tender Joint Count (TJC), Swollen Joint Count (SJC), and at least 3 of the 5 remaining core set measures: 1) Health Assessment Questionnaire-Disability Index (HAQ-DI), 2) C-reactive Protein (CRP), 3) Patient's Assessment of Arthritis Pain-Visual Analog Scale (PAAP-VAS), 4) Patient's Global Assessment of Disease Activity-Visual Analog Scale (PtGADA-VAS), 5) Physician's Global Assessment of Disease Activity-Visual Analog Scale (PhGA-VAS).

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

End point timeframe:

Week 6

| End point values | CZP+MTX (FAS) | ADA+MTX (FAS) | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 454 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 64.5 | 60.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 6

| | |
|-----------------|---|
| End point title | Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 6 |
|-----------------|---|

End point description:

DAS28 [ESR] was calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC), Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual

Analog Scale (PtGADA-VAS in mm) using the following formula: $0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \log_{10}(\text{ESR}) + 0.014 \times \text{Patient Global Assessment of Arthritis}$, where 28 joints were examined and a lower score indicates less disease activity.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 6 | |

| End point values | CZP+MTX (FAS) | ADA+MTX (FAS) | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 454 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 20.5 | 18.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 12

| | |
|-----------------|---|
| End point title | Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 12 |
|-----------------|---|

End point description:

DAS28 [ESR] was calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC), Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula: $0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \log_{10}(\text{ESR}) + 0.014 \times \text{Patient Global Assessment of Arthritis}$, where 28 joints were examined and a lower score indicates less disease activity.

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

| End point values | CZP+MTX (FAS) | ADA+MTX (FAS) | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 454 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 30.4 | 29.7 | | |

Statistical analyses

Secondary: Percentage of subjects with a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) \leq 3.2 at Week 104, in subjects responding at both Week 6 and Week 12

| | |
|-----------------|--|
| End point title | Percentage of subjects with a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) \leq 3.2 at Week 104, in subjects responding at both Week 6 and Week 12 |
|-----------------|--|

End point description:

DAS28 [ESR] was calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC), Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula: $0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.70 \times \log_{10}(\text{ESR}) + 0.014 \times \text{Patient Global Assessment of Arthritis}$, where 28 joints were examined and a lower score indicates less disease activity.

The definition of Week 6/12 responders was DAS28[ESR] Low Disease Activity (LDA) (ie ≤ 3.2) or an improvement of ≥ 1.2 in DAS28[ESR] relative to Baseline.

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

End point timeframe:

Week 104

| End point values | CZP+MTX (Week 12 Responder Set) | ADA+MTX (Week 12 Responder Set) | | |
|-------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 310 | 298 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of subjects | 47.7 | 46.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 104

| | |
|-----------------|---|
| End point title | Change from Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 104 |
|-----------------|---|

End point description:

HAQ-DI was derived based on the mean of individual scores in 8 categories of daily living activities (using 20 questions). Each question was scored 0-3 (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do), and the total HAQ-DI was scored on the scale of 0-3 as well. Change from Baseline was computed as the value at Week 104 minus the Baseline value. A negative value in Change from Baseline indicates an improvement.

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

End point timeframe:

From Baseline to Week 104

| End point values | CZP+MTX (FAS) | ADA+MTX (FAS) | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 454 | | |
| Units: Units on a Scale | | | | |
| least squares mean (standard error) | | | | |
| Least squares mean | -0.62 (± 0.03) | -0.72 (± 0.03) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of Proportion of Subjects Who Discontinued After Response at Week 12

| | |
|------------------------|--|
| End point title | Kaplan-Meier Estimates of Proportion of Subjects Who Discontinued After Response at Week 12 |
| End point description: | Response at Week 12 means that a subject had either a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 12 or had a reduction of DAS28 [ESR] ≥ 1.2 from Baseline to Week 12. Kaplan-Meier Estimates of Proportion of Subjects Discontinued are presented per study week (days relative to Week 12 visit). |
| End point type | Secondary |
| End point timeframe: | From Week 12 up to Week 104 |

| End point values | CZP+MTX (Week 12 Responder Set) | ADA+MTX (Week 12 Responder Set) | | |
|-------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 353 | 361 | | |
| Units: proportion of subjects | | | | |
| number (not applicable) | | | | |
| Week 13 (Day 7) | 0 | 0.0028 | | |
| Week 26 (Day 98) | 0.0198 | 0.0332 | | |
| Week 39 (Day 189) | 0.0453 | 0.0609 | | |
| Week 52 (Day 280) | 0.0963 | 0.0886 | | |
| Week 65 (Day 371) | 0.1643 | 0.1607 | | |
| Week 78 (Day 462) | 0.2181 | 0.1967 | | |
| Week 91 (Day 553) | 0.2408 | 0.2105 | | |
| Week 104 (Day 644) | 0.2635 | 0.2247 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the entire study period (From Week -4 to Week 104).

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | CZP+MTX (SS) |
|-----------------------|--------------|

Reporting group description:

All subjects who received at least 1 dose of Certolizumab pegol (CZP).

All adverse events that occurred when the subject was receiving CZP treatment are summarized in this group.

| | |
|-----------------------|--------------|
| Reporting group title | ADA+MTX (SS) |
|-----------------------|--------------|

Reporting group description:

All subjects who received at least 1 dose of Adalimumab (ADA).

All adverse events that occurred when the subject was receiving ADA treatment are summarized in this group.

| Serious adverse events | CZP+MTX (SS) | ADA+MTX (SS) | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 67 / 516 (12.98%) | 58 / 523 (11.09%) | |
| number of deaths (all causes) | 3 | 3 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Borderline mucinous tumour of ovary | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ovarian adenoma | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Venous thrombosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral venous disease | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Osteosynthesis | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy with contraceptive device | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| General disorders and administration site conditions | | | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 2 / 523 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Adjustment disorder | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural heamatoma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Ophthalmic vein thrombosis subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diplopia subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Obstruction gastric subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic gastritis subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Irritable bowel syndrome subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal stenosis subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anorectal varices | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 2 / 523 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 4 / 523 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Bone disorder | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Torticollis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 516 (0.58%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon disorder | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Mycobacterial infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 516 (0.39%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 2 / 523 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oophoritis | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis A | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 516 (0.19%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 516 (1.16%) | 5 / 523 (0.96%) | |
| occurrences causally related to treatment / all | 2 / 6 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 516 (0.19%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 0 / 523 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 516 (0.39%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 516 (0.00%) | 1 / 523 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | CZP+MTX (SS) | ADA+MTX (SS) | |
|---|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 269 / 516 (52.13%) | 244 / 523 (46.65%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 37 / 516 (7.17%) | 31 / 523 (5.93%) | |
| occurrences (all) | 42 | 34 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 55 / 516 (10.66%) | 47 / 523 (8.99%) | |
| occurrences (all) | 62 | 77 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 31 / 516 (6.01%) | 23 / 523 (4.40%) | |
| occurrences (all) | 36 | 26 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 21 / 516 (4.07%) | 28 / 523 (5.35%) | |
| occurrences (all) | 26 | 35 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 79 / 516 (15.31%) | 67 / 523 (12.81%) | |
| occurrences (all) | 116 | 106 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 53 / 516 (10.27%) | 60 / 523 (11.47%) | |
| occurrences (all) | 74 | 80 | |

| | | | |
|-----------------------------|------------------|------------------|--|
| Urinary tract infection | | | |
| subjects affected / exposed | 43 / 516 (8.33%) | 51 / 523 (9.75%) | |
| occurrences (all) | 58 | 65 | |
| Latent tuberculosis | | | |
| subjects affected / exposed | 31 / 516 (6.01%) | 27 / 523 (5.16%) | |
| occurrences (all) | 31 | 27 | |
| Sinusitis | | | |
| subjects affected / exposed | 31 / 516 (6.01%) | 21 / 523 (4.02%) | |
| occurrences (all) | 35 | 31 | |
| Bronchitis | | | |
| subjects affected / exposed | 29 / 516 (5.62%) | 25 / 523 (4.78%) | |
| occurrences (all) | 33 | 26 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 07 May 2012 | <p>The main purpose was to address operational challenges, changes were considered practical, not to carry excess risk to the study subjects, and to have minimal impact on the study outcome.</p> <p>The changes included:</p> <ul style="list-style-type: none">•Washout Periods for analgesic and nonbiologic DMARDs were added to clarify subject eligibility.•Upper limit of eligibility for the liver function tests (LFTs) was increased to >1.5 times since many subjects in the targeted population were taking medications that can cause modest elevations in LFTs. RA is also an inflammatory process, whereby subjects may also have modestly elevated LFTs.•The definition of an inadequate response to MTX was revised to align with clinical practice.•Adjustments to MTX doses and oral corticosteroid doses were permitted during the study.•Revisions to the exclusion criterion that listed bacteria/fungal infections, due to false negative rate associated with various serological tests as well as the lack of specificity provided by chest x-rays with respect to granulomatous changes.•Clarification of the definitions of a positive and negative purified protein derivative test, to minimize the risk of missing a subject with possible LTB infection.•Addition of -cotinine level measurement, as a validated marker of exposure to smoking, since smoking exposure is linked to an increase risk of developing RA, and exposure to smoking also impedes the effectiveness of biologic DMARDs. -extra sampling time points for IMP antibody determination and in particular for the genomic analysis were included to allow for early detection of IMP antibodies and genomic biomarkers.•Since prior anti-TNF use was an exclusion criterion, this class of medication was removed as a covariate in the primary efficacy analysis.•Changes were implemented to minimize/eliminate the confounding effect of substance abuse, since recreational drugs frequently can induce expectations or effects that may enhance or mask a disease entity under study such as pain. |
| 19 October 2012 | <p>The main purpose of this protocol amendment was to update all procedures related to tuberculosis (TB) detection and monitoring in line with the revised UCB policy.</p> <p>The amended changes also included updates of a number of eligibility criteria, specifically:</p> <ul style="list-style-type: none">•Clarification of the required clinical parameters to define moderate to severe RA disease at Screening and Baseline and the duration of the Washout Periods for analgesics and nonbiologic DMARDs.•The upper limit of eligibility for the LFTs was increased to >2.0 times since RA is an inflammatory process that may lead to modestly elevated LFTs and many subjects in the targeted population were taking medications, which can also cause modest elevations in LFTs. <p>Study procedure revisions included:</p> <ul style="list-style-type: none">•Any safety laboratory parameter could be repeated when the result was considered erroneous in the judgment of the Investigator or if it was known that the sample could have been mishandled.•The number of sampling times for the genomic analysis was reduced.•The definition of an inadequate response to MTX was revised to emphasize that the decision was based on the Investigator's clinical judgment. |

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| 24 July 2013 | <p>The main purpose was to provide further clarification to support interpretation. The clarifications included:</p> <ul style="list-style-type: none"> •Dose adjustments of oral corticosteroids during the 28 days prior to Baseline were to be avoided unless clinically necessary. The respective language was updated for clarity. Guidelines for discontinuation/tapering of oral corticosteroids permitted during the study were amended with more details •Guidance to ensure an appropriate washout of prior medication was updated for clarity and also specified information regarding the washout of leflunomide •RA-related exclusion criteria were updated with more specific information regarding subjects with systemic lupus erythematosus, lupus nephritis, and Sjogren's Syndrome •Duration of exclusionary periods for subjects with a history of chronic/recurrent infections was decreased to 6 months preceding the study for subjects with more than 3 episodes requiring antibiotics/antivirals and increased to 12 months prior to Baseline for subjects with recent serious/life-threatening infection •Exclusion criterion related to a history/active systemic/respiratory infection was updated with more details regarding radiographic findings •Guidance for the exclusion of subjects with hepatitis B or C infection including assessments of hepatitis-related biomarkers and for subjects with any positive findings in the urine drug screen •Noncompliance with the protocol-defined visit schedule was a reason for withdrawal. This withdrawal criterion was updated to provide additional guidance •Amendment of inclusion criterions to further emphasize that abstinence was not considered an acceptable method •Addition of albumin and creatinine to the list of clinical chemistry parameters •Update of the <ul style="list-style-type: none"> -list of the most common adverse reactions in clinical studies of ADA to match the latest version of the ADA SmPC -section describing the handling of protocol deviations to reflect process related changes resulting from the Submission Excellence Program |
| 26 March 2014 | <p>The main purposes were:</p> <ul style="list-style-type: none"> •To clarify the timing of the primary endpoint analyses •To note how unblinding of individual treatment allocation codes were to be handled at the Week 104/WD visit <p>The analysis of data for the Week 12 and Week 104 primary endpoints was changed to be done only at the completion of the study. The reason for this change was that knowledge of the Week 12 efficacy results could bias the way that the Investigators and/or subjects performed assessments or completed the study, which could compromise the interpretation of the final results and/or conclusions.</p> <p>Once all the efficacy assessments were performed for an individual subject at Week 104/WD, the blinded team had the opportunity to unblind the treatment allocation code for that subject. The reason was to aid the Investigator's decision regarding RA treatment after the study. To confirm that this by subject-unblinding did not impact the study results, a sensitivity analysis was added in which all subjects who had their TJC/SJC values at Week 104/WD changed post-visit were excluded.</p> <p>Other changes were:</p> <ul style="list-style-type: none"> •Modification of text relating to storage and handling of study drugs. •Blood sampling for cotinine at withdrawal did not need to be done if the withdrawal was due to the subject being ineligible to continue in the study at Week 24. •Clarification that all chest radiographs had to be both read and reported by a qualified radiologist. •Addition of text regarding the method of documentation of RA treatment after Week 104/WD. •The ISRQ/SIAQ was performed throughout the study as planned. However, statistical analysis of these questionnaires might not be performed for data at later time points in the study, because the available commercial ADA had undergone an alteration of the needle gauge during this study, which could affect the responses of the subjects to these questionnaires. •Addition of analysis sets needed for selected analyses based on subjects that reached Week 12 and continued in the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported