



Clinical trial results:

A Phase 3B, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Abatacept SC in Combination with Methotrexate Compared to Methotrexate Monotherapy in Achieving Clinical Remission in Adults with Early Rheumatoid Arthritis who are Methotrexate Naive

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2015-001275-50 |
| Trial protocol | CZ AT DE GB HU SE FR FI ES NL RO IT |
| Global end of trial date | 19 March 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 04 April 2021 |
| First version publication date | 04 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | IM101-550 |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to compare the clinical efficacy of weekly abatacept in combination with MTX to MTX alone in achieving Remission, defined as SDAI \leq 3.3, at Week 24.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 31 August 2015 |
| 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 | Argentina: 141 |
| Country: Number of subjects enrolled | Australia: 23 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Brazil: 110 |
| Country: Number of subjects enrolled | Canada: 24 |
| Country: Number of subjects enrolled | Colombia: 66 |
| Country: Number of subjects enrolled | Finland: 4 |
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Hungary: 40 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | Korea, Republic of: 16 |
| Country: Number of subjects enrolled | Monaco: 4 |
| Country: Number of subjects enrolled | Mexico: 154 |
| Country: Number of subjects enrolled | Peru: 59 |
| Country: Number of subjects enrolled | Poland: 41 |
| Country: Number of subjects enrolled | Qatar: 4 |
| Country: Number of subjects enrolled | Romania: 1 |
| Country: Number of subjects enrolled | Russian Federation: 40 |
| Country: Number of subjects enrolled | Singapore: 4 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Sweden: 7 |
| Country: Number of subjects enrolled | United States: 239 |
| Country: Number of subjects enrolled | Chile: 70 |
| Country: Number of subjects enrolled | Czechia: 39 |
| Country: Number of subjects enrolled | Germany: 69 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | Japan: 124 |
| Country: Number of subjects enrolled | Taiwan: 19 |
| Country: Number of subjects enrolled | South Africa: 63 |
| Worldwide total number of subjects | 1458 |
| EEA total number of subjects | 261 |

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) | 1254 |
| From 65 to 84 years | 202 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

994 treated in the induction period (IP). 184 from IP randomized and treated in De-Escalation (DeE), 685 treated in the Open Label (OL) and 120 treated in the Open Label Extension (OLE) period. Subjects (pt) in IP could move to the OL period after IP completion or through early IP escape. PT from DeE could transfer to OL or to OLE.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) |

Arm description:

Abatacept 125 mg subcutaneous injection once per week + Methotrexate at least 15mg per week tablet or capsule orally once per week

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

Dosage and administration details:

SC 125mg in 1ml pre-filled syringes

| | |
|--|--------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2.5 mg Tablet

| | |
|------------------|---------------------------------------|
| Arm title | Placebo + Methotrexate (Cohort 1, IP) |
|------------------|---------------------------------------|

Arm description:

Placebo of Abatacept 125 mg subcutaneous injection once per week + Methotrexate at least 15mg per week tablet or capsule orally once per week

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

Dosage and administration details:

SC placebo in 1ml pre-filled syringes

| | |
|---|--|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 2.5 mg Tablet | |
| Arm title | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) |
| Arm description: | |
| Active abatacept SC (125 mg) weekly + methotrexate weekly | |
| Arm type | Experimental |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 2.5 mg Tablet | |
| Investigational medicinal product name | Abatacept |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| SC 125mg in 1ml pre-filled syringes | |

| Number of subjects in period 1 ^[1] | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) | Placebo + Methotrexate (Cohort 1, IP) | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) |
|---|--|---------------------------------------|--|
| | | | |
| Started | 451 | 301 | 242 |
| Induction to Open Label (OL) | 289 ^[2] | 196 ^[3] | 147 ^[4] |
| Early Escaped to Open Label | 10 ^[5] | 21 ^[6] | 8 ^[7] |
| Induction to De-Escalation (DeE) | 94 ^[8] | 37 ^[9] | 53 ^[10] |
| Completed | 388 | 233 | 201 |
| Not completed | 63 | 68 | 41 |
| Withdrawal of Consent | 11 | 10 | 3 |
| Adverse event, serious fatal | 1 | 1 | - |
| No Longer Meets Study Criteria | 2 | 3 | - |
| Poor/Non-Compliance | 3 | 2 | 3 |
| Not Disclosed | 1 | - | 2 |
| Adverse event, non-fatal | 18 | 8 | 14 |
| Pregnancy | 2 | - | - |
| Lost to follow-up | 3 | 6 | 4 |
| Subject Request to Discontinue | 11 | 3 | 6 |

| | | | |
|------------------|----|----|---|
| Lack of efficacy | 11 | 35 | 9 |
|------------------|----|----|---|

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 994 subjects enrolled and treated

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents subjects who transitioned to DeEscalation or Open label periods

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Inclusive of all treatments, all periods

| Reporting group values | Overall Study | Total | |
|--|---------------|-------|--|
| Number of subjects | 994 | 994 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 865 | 865 | |
| From 65-84 years | 129 | 129 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 49.1 | | |
| standard deviation | ± 13.17 | - | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 781 | 781 | |
| Male | 213 | 213 | |
| Race | | | |
| Units: Subjects | | | |
| WHITE | 698 | 698 | |
| BLACK/AFRICAN AMERICAN | 43 | 43 | |
| AMERICAN INDIAN/ALASKA NATIVE | 4 | 4 | |
| ASIAN | 140 | 140 | |
| RACE - OTHER/ NOT REPORTED | 109 | 109 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 22 | 22 | |
| Not Hispanic or Latino | 112 | 112 | |
| Ethnicity not reported | 860 | 860 | |
| MODIFIED SHARP/VAN DER HEIJDE TOTAL SCORE (mTSS) | | | |
| The Modified Total Sharp Score (mTSS) is calculated as the bilateral sum of erosion and Joint Space Narrowing (JSN) scores across all joints of the hands and feet. The score range for mTSS is 0-448. Higher scores indicate more joint damage. | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 11.08 | | |
| standard deviation | ± 17.839 | - | |
| Tender Joints - 28 | | | |
| number of painful joints from 28 joints | | | |
| Units: Joint Count | | | |
| arithmetic mean | 13.4 | | |
| standard deviation | ± 6.76 | - | |
| Swollen Joints - 28 | | | |
| number of swollen joints from 28 joints | | | |
| Units: Joint Count | | | |
| arithmetic mean | 10.3 | | |

| | | | |
|---|----------|---|--|
| standard deviation | ± 5.77 | - | |
| Subject global assessment of disease activity | | | |
| Subject's global assessment of disease activity by using a Visual Analog Scale (VAS). The scale ranges from 0 mm to 100 mm, [0 mm=no pain to 100 mm=worst possible pain] | | | |
| Units: mm | | | |
| arithmetic mean | 64.5 | | |
| standard deviation | ± 23.28 | - | |
| Physician global assessment of disease activity | | | |
| physician's global assessment of disease activity using a Visual Analog Scale (VAS). The scale ranges from 0 to 100 mm, [0=no arthritis activity to 100 =extremely active arthritis] | | | |
| Units: mm | | | |
| arithmetic mean | 65.5 | | |
| standard deviation | ± 18.99 | - | |
| C-Reactive Protein (CRP) | | | |
| Units: mg/dL | | | |
| arithmetic mean | 1.960 | | |
| standard deviation | ± 2.5129 | - | |
| DAS28-CRP | | | |
| The Disease Activity Score (DAS28-CRP) =0.56×sqrt(tender joints [count:1-28])+0.28×sqrt(swollen joints [count:1-28])+0.36×Ln(CRP level+1)+0.014×(patient's disease assessment on 0-100 mm scale [100=most severe])+0.96. Range: 0.96 to no upper limit. Higher score=more severe disease. | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 5.58 | | |
| standard deviation | ± 1.049 | - | |
| SDAI | | | |
| Simple Disease Activity Index is the numerical sum of five outcome parameters: tender joint count and swollen joint count based on a 28-joint assessment, patient global assessment and physician global assessment assessed on a visual analogue scale scale (range 0 to 10 cm), and C-reactive protein measured in mg/dL. SDAI total score range: 0 to 86. SDAI ≤ 3.3 indicates disease remission and SDAI >26 = high disease activity. | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 38.69 | | |
| standard deviation | ± 13.961 | - | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) |
| Reporting group description: Abatacept 125 mg subcutaneous injection once per week + Methotrexate at least 15mg per week tablet or capsule orally once per week | |
| Reporting group title | Placebo + Methotrexate (Cohort 1, IP) |
| Reporting group description: Placebo of Abatacept 125 mg subcutaneous injection once per week + Methotrexate at least 15mg per week tablet or capsule orally once per week | |
| Reporting group title | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) |
| Reporting group description: Active abatacept SC (125 mg) weekly + methotrexate weekly | |

Primary: Percentage of participants in Simple Disease Activity Index (SDAI) remission at Week 24

| | |
|--|---|
| End point title | Percentage of participants in Simple Disease Activity Index (SDAI) remission at Week 24 |
| End point description: Simple Disease Activity Index (SDAI) is calculated using the following formula: TJC + SJC + PGA + MDGA + CRP (TJC = number of painful joints from 28 joints, SJC = number of swollen joints from 28 joints, PGA = patient global assessment on a visual analog scale 0-10 cm, MDGA = physician global assessment on a visual analog scale 0-10 cm, and CRP = c-reactive protein in mg/dL) SDAI Remission is defined as SDAI ≤ 3.3. Using a logistic regression model that includes treatment arm, randomization stratification factor, and baseline SDAI as continuous variable and point estimate of adjusted ORs, corresponding 95% CI and p-value was provided. SDAI total score range: 0 to 86. SDAI ≤ 3.3 indicates disease remission and SDAI >26 = high disease activity. | |
| End point type | Primary |
| End point timeframe: Week 24 | |

| End point values | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) | Placebo + Methotrexate (Cohort 1, IP) | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) | |
|-----------------------------------|--|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 150 | 0 ^[1] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 21.3 (16.0 to 26.7) | 16.0 (10.1 to 21.9) | (to) | |

Notes:

[1] - Arm is not part of the Analysis population

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | SDAI at 24 weeks |
| Comparison groups | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) v Placebo + Methotrexate (Cohort 1, IP) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 375 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2359 |
| Method | Regression, Logistic |

Secondary: Percentage of participants in Disease Activity Score (DAS)28 - c-reactive protein (CRP) remission at Week 24

| | |
|---|--|
| End point title | Percentage of participants in Disease Activity Score (DAS)28 - c-reactive protein (CRP) remission at Week 24 |
| End point description: DAS28-CRP = Disease Activity Score 28 based on C-reactive protein DAS28-CRP Remission is defined as DAS28-CRP ≤ 2.6 Using a logistic regression model that includes treatment arm, stratification variable and baseline measure as continuous variable and point estimate of adjusted ORs, corresponding 95% CI and p-value was provided. | |
| End point type | Secondary |
| End point timeframe: Week 24 | |

| End point values | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) | Placebo + Methotrexate (Cohort 1, IP) | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) | |
|-----------------------------------|--|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 150 | 0 ^[2] | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 38.7 (32.3 to 45.0) | 25.3 (18.4 to 32.3) | (to) | |

Notes:

[2] - Arm is not part of the Analysis population

Statistical analyses

| | |
|---|--|
| Statistical analysis title | DAS 28 |
| Comparison groups | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) v Placebo + Methotrexate (Cohort 1, IP) |
| Number of subjects included in analysis | 375 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0112 |
| Method | Regression, Logistic |

Secondary: Percentage of participants in SDAI remission at Week 52

| | |
|-----------------|---|
| End point title | Percentage of participants in SDAI remission at Week 52 |
|-----------------|---|

End point description:

Simple Disease Activity Index (SDAI) is calculated using the following formula: TJC + SJC + PGA + MDGA + CRP (TJC = number of painful joints from 28 joints, SJC = number of swollen joints from 28 joints, PGA = patient global assessment on a visual analog scale 0-10 cm, MDGA = physician global assessment on a visual analog scale 0-10 cm, and CRP = c-reactive protein in mg/dL) SDAI Remission is defined as SDAI \leq 3.3. Using a logistic regression model that includes treatment arm, randomization stratification factor, and baseline SDAI as continuous variable and point estimate of adjusted ORs, corresponding 95% CI and p-value was provided. SDAI total score range: 0 to 86. SDAI \leq 3.3 indicates disease remission and SDAI >26 = high disease activity.

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

End point timeframe:

Week 52

| End point values | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) | Placebo + Methotrexate (Cohort 1, IP) | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) | |
|-----------------------------------|--|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 150 | 0 ^[3] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 29.8 (23.8 to 35.8) | 15.3 (9.6 to 21.1) | (to) | |

Notes:

[3] - Arm is not part of the Analysis population

Statistical analyses

| | |
|---|--|
| Statistical analysis title | SDAI at 52 weeks |
| Comparison groups | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) v Placebo + Methotrexate (Cohort 1, IP) |
| Number of subjects included in analysis | 375 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0021 |
| Method | Regression, Logistic |

Secondary: Mean change from baseline in radiographic progression of joint damage as measured by modified Sharp/van der Heijde Total Sharp scores (TSS) at Week 52

| | |
|-----------------|--|
| End point title | Mean change from baseline in radiographic progression of joint damage as measured by modified Sharp/van der Heijde Total Sharp scores (TSS) at Week 52 |
|-----------------|--|

End point description:

The Modified Total Sharp Score (mTSS) is calculated as the bilateral sum of erosion and Joint Space Narrowing (JSN) scores across all joints of the hands and feet. The score range for mTSS is 0-448. Higher scores indicate more joint damage. The mean change from baseline in TSS using modified Sharp/van der Heijde scores was assessed using a rank-based nonparametric ANCOVA model.

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

End point timeframe:

Week 52

| End point values | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) | Placebo + Methotrexate (Cohort 1, IP) | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) | |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 401 | 249 | 0 ^[4] | |
| Units: Total Sharp Score | | | | |
| arithmetic mean (standard deviation) | 0.53 (± 2.279) | 2.52 (± 6.205) | () | |

Notes:

[4] - Arm is not part of the Analysis population

Statistical analyses

| Statistical analysis title | TTS |
|---|--|
| Comparison groups | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) v Placebo + Methotrexate (Cohort 1, IP) |
| Number of subjects included in analysis | 650 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | rank-based ANCOVA |

Secondary: Percentage of participants in Boolean remission at Week 52

| End point title | Percentage of participants in Boolean remission at Week 52 |
|---|--|
| End point description: | |
| Boolean Remission is defined as Tender joint count less than 1, Swollen joint count less than 1, CRP less than 1 mg/dL, patient global assessment less than 1 (on 0 to 10 VAS scale). Logistic regression was used for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) | Placebo + Methotrexate (Cohort 1, IP) | Combination Therapy: Abatacept + Methotrexate (Cohort 2, IP) | |
|-----------------------------------|--|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 451 | 301 | 0 ^[5] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 21.5 (17.7 to 25.3) | 11.6 (8.0 to 15.2) | (to) | |

Notes:

[5] - Arm is not part of the Analysis population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Boolean Remission |
| Comparison groups | Combination Therapy: Abatacept + Methotrexate (Cohort 1, IP) v Placebo + Methotrexate (Cohort 1, IP) |
| Number of subjects included in analysis | 752 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0006 |
| Method | Regression, Logistic |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from start of treatment up to 56 days after last treatment.

Adverse event reporting additional description:

Randomization of DeE lead to 4 arms: Aba Weekly + MTX(50 subjects), Aba EoW + MTX (50 subjects), Aba Mono (47 subjects) , MTX alone (37 subjects) which had a total of 184 subjects.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Cohort 1:Aba + MTX |
|-----------------------|--------------------|

Reporting group description:

Subjects received abatacept 125 milligram (mg) subcutaneously (sc) with a combination of methotrexate of at least 15 mg tablet administered orally once per week (qw) up to week 24.

| | |
|-----------------------|--------------------|
| Reporting group title | Cohort 1:MTX Alone |
|-----------------------|--------------------|

Reporting group description:

Subjects received abatacept matching placebo 125 mg sc with a combination of methotrexate of at least 15 mg tablet administered orally qw up to week 24.

| | |
|-----------------------|--------------------|
| Reporting group title | Cohort 2:Aba + MTX |
|-----------------------|--------------------|

Reporting group description:

Subjects received abatacept 125 mg sc with a combination of methotrexate of at least 15 mg tablet administered orally qw up to week 56.

| | |
|-----------------------|------------------|
| Reporting group title | Aba Weekly + MTX |
|-----------------------|------------------|

Reporting group description:

Subjects who completed the 56 week Induction Period were randomized to this De-escalation Period received abatacept 125 mg sc with a combination of methotrexate of at least 15 mg tablet administered orally qw up to week 104.

| | |
|-----------------------|---------------|
| Reporting group title | Aba EOW + MTX |
|-----------------------|---------------|

Reporting group description:

Subjects who completed the 56 week Induction Period were randomized to this De-escalation Period received abatacept 125 mg sc every other week (EOW) alternating with a matching placebo of abatacept with a combination of methotrexate of at least 15 mg tablet administered orally weekly up to week 80.

| | |
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| Reporting group title | Aba Mono |
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Reporting group description:

Subjects who completed the 56 week Induction Period were randomized to this De-escalation Period received abatacept 125 mg sc with a combination of methotrexate matching placebo of at least 15 mg tablet administered orally weekly up to week 104.

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| Reporting group title | MTX Alone |
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Reporting group description:

Subjects who completed the 56 week Induction Period were randomized to this De-escalation Period received abatacept matching placebo 125 mg sc with a combination of methotrexate of at least 15 mg tablet administered orally weekly up to week 104.

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| Reporting group title | OL Aba + MTX |
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Reporting group description:

Subjects who completed the 104 week of treatment entered Open-Label Period received abatacept 125 mg sc with a combination of methotrexate matching placebo of at least 15 mg tablet administered orally qw up to week 104.

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| Reporting group title | OLE Aba |
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Reporting group description:

Subjects who completed the Induction Period and De-escalation Period with escape or remission entered 24 week optional Open Label Extension Period and received abatacept 125 mg sc qw up to week 128.

| Serious adverse events | Cohort 1:Aba + MTX | Cohort 1:MTX Alone | Cohort 2:Aba + MTX |
|---|---------------------------|---------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 32 / 451 (7.10%) | 9 / 301 (2.99%) | 23 / 242 (9.50%) |
| number of deaths (all causes) | 1 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Carcinoid tumour of the gastrointestinal tract | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign ovarian tumour | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 1 / 301 (0.33%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Knee operation | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrometra | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metrorrhagia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal polyp | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 2 / 451 (0.44%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture displacement | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoconiosis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 1 / 301 (0.33%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 1 / 301 (0.33%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar stroke | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxic-Ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular degeneration | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular hole | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malocclusion | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 2 / 242 (0.83%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 451 (0.44%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 1 / 301 (0.33%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 1 / 301 (0.33%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Exostosis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 1 / 301 (0.33%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 451 (0.44%) | 2 / 301 (0.66%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 1 / 301 (0.33%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 451 (0.44%) | 1 / 301 (0.33%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilus infection | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 451 (0.00%) | 0 / 301 (0.00%) | 1 / 242 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Aba Weekly + MTX | Aba EOW + MTX | Aba Mono |
|---|------------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Carcinoid tumour of the gastrointestinal tract | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign ovarian tumour | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Knee operation | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrometra | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal polyp | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Fracture displacement | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoconiosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar stroke | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxic-Ischaemic encephalopathy | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular degeneration | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular hole | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malocclusion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exostosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilus infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | MTX Alone | OL Aba + MTX | OLE Aba |
|---|----------------|------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 40 / 685 (5.84%) | 0 / 120 (0.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Carcinoid tumour of the gastrointestinal tract | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign ovarian tumour | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Knee operation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrometra | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal polyp | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture displacement | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoconiosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Skin laceration | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar stroke | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxic-Ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 685 (0.29%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular degeneration | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Macular hole | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malocclusion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exostosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 685 (0.29%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilus infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 685 (0.15%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 685 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Cohort 1:Aba + MTX | Cohort 1:MTX Alone | Cohort 2:Aba + MTX |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 237 / 451 (52.55%) | 152 / 301 (50.50%) | 123 / 242 (50.83%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 24 / 451 (5.32%) | 15 / 301 (4.98%) | 10 / 242 (4.13%) |
| occurrences (all) | 33 | 20 | 11 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 14 / 451 (3.10%) | 10 / 301 (3.32%) | 9 / 242 (3.72%) |
| occurrences (all) | 16 | 14 | 11 |
| Influenza a virus test positive | | | |
| subjects affected / exposed | 1 / 451 (0.22%) | 0 / 301 (0.00%) | 0 / 242 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 451 (2.44%) | 8 / 301 (2.66%) | 5 / 242 (2.07%) |
| occurrences (all) | 11 | 8 | 5 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 31 / 451 (6.87%) | 21 / 301 (6.98%) | 8 / 242 (3.31%) |
| occurrences (all) | 38 | 24 | 12 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 451 (2.66%) | 18 / 301 (5.98%) | 4 / 242 (1.65%) |
| occurrences (all) | 12 | 22 | 5 |
| General disorders and administration site conditions | | | |
| Drug intolerance | | | |
| subjects affected / exposed | 7 / 451 (1.55%) | 4 / 301 (1.33%) | 0 / 242 (0.00%) |
| occurrences (all) | 7 | 5 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 42 / 451 (9.31%) | 24 / 301 (7.97%) | 22 / 242 (9.09%) |
| occurrences (all) | 56 | 27 | 25 |
| Stomatitis | | | |
| subjects affected / exposed | 27 / 451 (5.99%) | 8 / 301 (2.66%) | 1 / 242 (0.41%) |
| occurrences (all) | 45 | 14 | 3 |
| Abdominal pain upper | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 12 / 451 (2.66%) 12 | 5 / 301 (1.66%) 6 | 14 / 242 (5.79%) 15 |
| Diarrhoea subjects affected / exposed occurrences (all) | 17 / 451 (3.77%) 17 | 12 / 301 (3.99%) 13 | 13 / 242 (5.37%) 17 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 15 / 451 (3.33%) 16 | 16 / 301 (5.32%) 17 | 13 / 242 (5.37%) 13 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 63 / 451 (13.97%) 81 | 43 / 301 (14.29%) 60 | 36 / 242 (14.88%) 47 |
| Pharyngitis subjects affected / exposed occurrences (all) | 22 / 451 (4.88%) 24 | 17 / 301 (5.65%) 19 | 14 / 242 (5.79%) 14 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 24 / 451 (5.32%) 28 | 16 / 301 (5.32%) 20 | 18 / 242 (7.44%) 18 |
| Bronchitis subjects affected / exposed occurrences (all) | 19 / 451 (4.21%) 20 | 12 / 301 (3.99%) 12 | 16 / 242 (6.61%) 20 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 13 / 451 (2.88%) 13 | 9 / 301 (2.99%) 10 | 10 / 242 (4.13%) 11 |
| Herpes zoster subjects affected / exposed occurrences (all) | 3 / 451 (0.67%) 3 | 2 / 301 (0.66%) 4 | 1 / 242 (0.41%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 17 / 451 (3.77%) 20 | 9 / 301 (2.99%) 13 | 13 / 242 (5.37%) 18 |

| Non-serious adverse events | Aba Weekly + MTX | Aba EOW + MTX | Aba Mono |
|--|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 12 / 50 (24.00%) | 22 / 50 (44.00%) | 10 / 47 (21.28%) |
| Investigations | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Influenza a virus test positive subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 50 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 3 / 50 (6.00%) 3 | 0 / 47 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 50 (2.00%) 1 | 1 / 47 (2.13%) 1 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| General disorders and administration site conditions Drug intolerance subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 2 / 50 (4.00%) 4 | 0 / 47 (0.00%) 0 |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 50 (2.00%) 1 | 2 / 47 (4.26%) 9 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Diarrhoea | | | |

| | | | |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 3 | 6 / 50 (12.00%) 7 | 4 / 47 (8.51%) 4 |
| Pharyngitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 50 (2.00%) 1 | 1 / 47 (2.13%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 2 / 50 (4.00%) 3 | 1 / 47 (2.13%) 1 |
| Bronchitis subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 6 / 50 (12.00%) 6 | 1 / 47 (2.13%) 1 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 3 / 50 (6.00%) 4 | 1 / 47 (2.13%) 1 |
| Herpes zoster subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 1 / 50 (2.00%) 1 | 1 / 47 (2.13%) 1 |

| Non-serious adverse events | MTX Alone | OL Aba + MTX | OLE Aba |
|--|---------------------|------------------------|----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 16 / 37 (43.24%) | 230 / 685 (33.58%) | 15 / 120 (12.50%) |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 20 / 685 (2.92%) 23 | 0 / 120 (0.00%) 0 |
| Aspartate aminotransferase | | | |

| | | | |
|---|---------------------|------------------------|----------------------|
| increased subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 11 / 685 (1.61%) 11 | 0 / 120 (0.00%) 0 |
| Influenza a virus test positive subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 1 / 685 (0.15%) 1 | 0 / 120 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 4 / 685 (0.58%) 4 | 0 / 120 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 20 / 685 (2.92%) 23 | 0 / 120 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 10 / 685 (1.46%) 11 | 1 / 120 (0.83%) 1 |
| General disorders and administration site conditions Drug intolerance subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 4 / 685 (0.58%) 4 | 0 / 120 (0.00%) 0 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 23 / 685 (3.36%) 24 | 0 / 120 (0.00%) 0 |
| Stomatitis subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 4 | 21 / 685 (3.07%) 31 | 2 / 120 (1.67%) 4 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 8 / 685 (1.17%) 9 | 1 / 120 (0.83%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 4 | 13 / 685 (1.90%) 15 | 1 / 120 (0.83%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|----------------------|------------------------|----------------------|
| Cough subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 11 / 685 (1.61%) 11 | 1 / 120 (0.83%) 1 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 37 (13.51%) 6 | 59 / 685 (8.61%) 75 | 6 / 120 (5.00%) 9 |
| Pharyngitis subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 18 / 685 (2.63%) 18 | 0 / 120 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 3 | 28 / 685 (4.09%) 31 | 3 / 120 (2.50%) 4 |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 24 / 685 (3.50%) 25 | 1 / 120 (0.83%) 1 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 13 / 685 (1.90%) 13 | 1 / 120 (0.83%) 1 |
| Herpes zoster subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 7 / 685 (1.02%) 7 | 0 / 120 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 26 / 685 (3.80%) 34 | 0 / 120 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 29 September 2015 | Incorporates changes in response to health authorities in countries participating in the Voluntary Harmonization Procedure (VHP) |
| 22 February 2016 | Provide clarifications of interpretation of the protocol and increase consistency in the protocol |
| 27 November 2017 | Added a new period (Optional Open Label Abatacept Extension for Subjects who Complete the DE Period); added a section 3.1.6.5 to describe the new period; added a sentence in Section 8.4.3, Safety analyses, to describe the analyses of those subjects. Updated the Medical Monitor Contact, added name of the Study Director, added abatacept/placebo and MTX reconciliation at Week 56 of IP, deleted BNP sample collection, added CRP collection at DE Week 64, added HAQ at Week 64, clarified corticosteroid rescue treatment to be for RA, corrected SAE reporting section. |
| 08 January 2018 | Corrected errors in Section 5.1, Table 5.1-6. Indicated the second phone call visit is at Week 112, deleted CRP testing at the office visits, added dosing of weekly SC abatacept, added diary cards will be collected at Week 116 and Week 128/ET, and indicated the office visit will be +/- 3 days of the target visit day. |
| 26 April 2018 | Updated the schematic in both the synopsis and body of the protocol to add the new optional open label SC abatacept period for DE completers. Added a paragraph in the synopsis to describe the optional open label SC abatacept period for DE completers. Modified the definition of serious breach. Two corrections made to Table 5.1-4 for procedures required at the ET or Final Visit. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported