



Clinical trial results:

A Phase 3, randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of four 12-week treatment cycles (48 weeks total) of epratuzumab in systemic lupus erythematosus subjects with moderate to severe disease

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-018565-26 |
| Trial protocol | HU ES DE GB IT |
| Global end of trial date | 03 June 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 18 June 2016 |
| First version publication date | 18 June 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | SL0010 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01261793 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB, Inc. |
| Sponsor organisation address | 1950 Lake Park Drive, Smyrna, United States, GA 30080 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 July 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 May 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to confirm the clinical efficacy of epratuzumab in the treatment of subjects with moderately to severely active Systemic Lupus Erythematosus (SLE) despite standard of care treatments (ie, corticosteroids and potentially antimalarials and immunosuppressants) continued from Baseline.

Protection of trial subjects:

Patients were pre-medicated prior to infusion of Investigational Medicinal Product (IMP) to prevent infusion reactions. During the conduct of the study all subjects were closely monitored.

Background therapy:

- Subjects must be receiving concomitant oral corticosteroids within the range of 5 to 60mg/day prednisone equivalents, dependent on the investigator's assessment of disease activity, at a stable dose for at least 5 days (± 1 day) prior to Week 0 (Visit 2) and the first study drug infusion. Tapering of oral corticosteroids after Week 4 (Visit 6) to a target dose of ≤ 7.5 mg/day prednisone equivalents is encouraged during the study.
- If the subject is receiving concomitant antimalarials, they must have been receiving them for at least 12 weeks prior to Screening/Baseline (Visit 1), with a stable dose regimen for at least 28 days (± 1 day) prior to Week 0 (Visit 2) and the first study drug infusion. The antimalarial dose should be continued at a stable dose (same as Baseline dose) during the study.
- If the subject is receiving concomitant immunosuppressants, they must be on a stable dose for at least 28 days (± 1 day) prior to Week 0 (Visit 2) and the first study drug infusion. The immunosuppressants dose should be continued at a stable dose (same as Baseline dose) during the study.
- Subjects receiving memantine, bromocriptine (Parlodel), danazol, dapson, dehydroepiandrosterone, or retinoids must be on a stable dose for 28 days (± 1 day) prior to Visit 2 and the first study drug infusion. The dose must remain stable during the study until Week 24 (Visit 14), after which time it may be held stable or decreased based on the investigator's judgment of the subject's disease activity and health status.

Evidence for comparator:

Not applicable

| | |
|---|------------------|
| Actual start date of recruitment | 22 December 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Brazil: 51 |
| Country: Number of subjects enrolled | Canada: 27 |
| Country: Number of subjects enrolled | France: 11 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Germany: 41 |
| Country: Number of subjects enrolled | Hungary: 44 |
| Country: Number of subjects enrolled | India: 4 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Mexico: 31 |
| Country: Number of subjects enrolled | Poland: 154 |
| Country: Number of subjects enrolled | Romania: 20 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | South Africa: 20 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Ukraine: 53 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | United States: 284 |
| Worldwide total number of subjects | 791 |
| EEA total number of subjects | 309 |

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) | 767 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in December 2010 and concluded in June 2015.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set.

Period 1

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo (RS) |

Arm description:

Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles

| | |
|--|-----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | Placebo |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

weekly

| | |
|------------------|---|
| Arm title | Epratuzumab 1200 mg every other week (RS) |
|------------------|---|

Arm description:

1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Epratuzumab |
| Investigational medicinal product code | Emab |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

600 mg every week, 1200 mg every other week

| | |
|------------------|----------------------------------|
| Arm title | Epratuzumab 600 mg per week (RS) |
|------------------|----------------------------------|

Arm description:

600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles

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

| | |
|--|-----------------------|
| Investigational medicinal product name | Epratuzumab |
| Investigational medicinal product code | Emab |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

600 mg every week, 1200 mg every other week

| Number of subjects in period 1 | Placebo (RS) | Epratuzumab 1200 mg every other week (RS) | Epratuzumab 600 mg per week (RS) |
|--|--------------|---|----------------------------------|
| | | | |
| Started | 263 | 262 | 266 |
| Completed | 178 | 171 | 184 |
| Not completed | 85 | 91 | 82 |
| Consent withdrawn by subject | 12 | 14 | 14 |
| AE(s), serious non-fatal | 5 | 12 | 10 |
| AE(s), serious fatal | 3 | 1 | - |
| AE(s), non-serious non-fatal | 4 | 11 | 8 |
| other | 4 | 7 | 4 |
| Lost to follow-up | 10 | 3 | 7 |
| Lack of efficacy | 44 | 37 | 32 |
| Protocol deviation | 3 | 5 | 6 |
| SAE(s), non-fatal and AE(s), non-serious non-fatal | - | 1 | 1 |

Baseline characteristics

Subject analysis sets

| | |
|--|--|
| Subject analysis set title | Placebo (Weekly infusion) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 1200 mg every other week |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: 1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 600 mg per week |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: 600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles | |
| Subject analysis set title | Placebo (Weekly infusion) FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 1200 mg every other week FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: 1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 600 mg per week FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: 600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles | |

| Reporting group values | Placebo (Weekly infusion) | Epratuzumab 1200 mg every other week | Epratuzumab 600 mg per week |
|---------------------------------------|---------------------------|--------------------------------------|-----------------------------|
| Number of subjects | 263 | 261 | 264 |
| Age Categorical Units: Subjects | | | |
| <=18 years | 0 | 4 | 3 |
| Adults (18-64 years) | 254 | 253 | 251 |
| >=65 years | 9 | 4 | 10 |
| Age Continuous Units: years | | | |
| arithmetic mean | 41.1 | 40.8 | 41.2 |
| standard deviation | ± 11.8 | ± 11.5 | ± 12.7 |
| Gender Categorical Units: Subjects | | | |
| Male | 18 | 14 | 19 |
| Female | 245 | 247 | 245 |

| Reporting group values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS |
|---|-------------------------------|--|---------------------------------|
| Number of subjects | 263 | 261 | 264 |
| Age Categorical Units: Subjects | | | |
| <=18 years Adults (18-64 years) >=65 years | | | |
| Age Continuous Units: years arithmetic mean standard deviation | ± | ± | ± |
| Gender Categorical Units: Subjects | | | |
| Male Female | | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Placebo (RS) |
| Reporting group description: Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles | |
| Reporting group title | Epratuzumab 1200 mg every other week (RS) |
| Reporting group description: 1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles | |
| Reporting group title | Epratuzumab 600 mg per week (RS) |
| Reporting group description: 600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles | |
| Subject analysis set title | Placebo (Weekly infusion) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 1200 mg every other week |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: 1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 600 mg per week |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: 600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles | |
| Subject analysis set title | Placebo (Weekly infusion) FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 1200 mg every other week FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: 1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles | |
| Subject analysis set title | Epratuzumab 600 mg per week FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: 600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles | |

Primary: The percent of subjects meeting treatment response criteria at Week 48 according to a combined response index

| | |
|------------------------|---|
| End point title | The percent of subjects meeting treatment response criteria at Week 48 according to a combined response index |
| End point description: | |
| End point type | Primary |

End point timeframe:

Week 48

| End point values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS | |
|-----------------------------|-------------------------------------|---|---------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 263 | 261 | 264 | |
| Units: percentage of | | | | |
| number (not applicable) | | | | |
| Responder | 33.5 | 34.1 | 35.2 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Comparison groups | Placebo (Weekly infusion) FAS v Epratuzumab 1200 mg every other week FAS |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.899 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.024 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.477 |

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Placebo (Weekly infusion) FAS v Epratuzumab 600 mg per week FAS |
| Number of subjects included in analysis | 527 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.716 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.743 |
| upper limit | 1.539 |

Secondary: The percent of subjects meeting treatment response criteria at Week 24 according to a combined response index

| | |
|-----------------|---|
| End point title | The percent of subjects meeting treatment response criteria at Week 24 according to a combined response index |
|-----------------|---|

End point description:

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

End point timeframe:

Week 24

| End point values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS | |
|-----------------------------|-------------------------------------|---|---------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 263 | 261 | 264 | |
| Units: percentage of | | | | |
| number (not applicable) | | | | |
| Responder | 32.3 | 33 | 43.6 | |

Statistical analyses

No statistical analyses for this end point

Secondary: The percent of subjects meeting treatment response criteria at Week 12 according to a combined response index

| | |
|-----------------|---|
| End point title | The percent of subjects meeting treatment response criteria at Week 12 according to a combined response index |
|-----------------|---|

End point description:

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

End point timeframe:

Week 12

| End point values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS | |
|-----------------------------|-------------------------------------|---|---------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 263 | 261 | 264 | |
| Units: percentage of | | | | |
| number (not applicable) | | | | |
| Responder | 30 | 32.2 | 40.9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: The percent of subjects meeting treatment response criteria at Week 36 according to a combined response index

| | |
|-----------------|---|
| End point title | The percent of subjects meeting treatment response criteria at Week 36 according to a combined response index |
|-----------------|---|

End point description:

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

End point timeframe:

Week 36

| End point values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS | |
|-----------------------------|-------------------------------------|---|---------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 263 | 261 | 264 | |
| Units: percentage of | | | | |
| number (not applicable) | | | | |
| Responder | 32.7 | 33 | 36.7 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in daily corticosteroid dose at Week 24

| | |
|-----------------|--|
| End point title | Change from Baseline in daily corticosteroid dose at Week 24 |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline, Week 24

| End point values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS | |
|---|-------------------------------------|---|---------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 263 | 261 | 264 | |
| Units: percentage of number (not applicable) | | | | |
| Dose decreased by >50% | 4.6 | 10 | 8.7 | |
| Dose decreased >0% to ≤50% | 20.9 | 18 | 18.2 | |
| No change in dose | 48.3 | 46.7 | 52.7 | |
| Dose increased or missing data | 26.2 | 25.3 | 20.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in daily corticosteroid dose at Week 48

| | |
|-----------------|--|
| End point title | Change from Baseline in daily corticosteroid dose at Week 48 |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline, Week 48

| End point values | Placebo (Weekly infusion) FAS | Epratuzumab 1200 mg every other week FAS | Epratuzumab 600 mg per week FAS | |
|---|-------------------------------------|---|---------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 263 | 261 | 264 | |
| Units: percentage of number (not applicable) | | | | |
| Dose decreased by >50% | 6.5 | 13.8 | 14.8 | |
| Dose decreased >0% to ≤50% | 20.9 | 13.4 | 15.9 | |
| No change in dose | 35.7 | 35.6 | 36.7 | |
| Dose increased or missing data | 36.9 | 37.2 | 32.6 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent Adverse Events (TEAEs) were collected during the course of the study, which started in December 2010 and concluded in June 2015. The Safety Set will be utilized for TEAE reporting.

Adverse event reporting additional description:

The Safety Set is all enrolled subjects who took at least 1 dose of study drug.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo (Weekly infusion) |
|-----------------------|---------------------------|

Reporting group description:

Placebo infusions delivered weekly for a total of 4 weeks over four 12-week treatment cycles

| | |
|-----------------------|-----------------------------|
| Reporting group title | Epratuzumab 600 mg per week |
|-----------------------|-----------------------------|

Reporting group description:

600 mg infusions delivered weekly for a total of 4 weeks (cumulative dose 2400 mg) over four 12 week treatment cycles

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Epratuzumab 1200 mg every other week |
|-----------------------|--------------------------------------|

Reporting group description:

1200 mg infusions delivered every other week for a total of 4 weeks (cumulative dose 2400 mg) over four 12-week treatment cycles and placebo infusions delivered every other week for a total of 4 weeks over four 12-week treatment cycles

| Serious adverse events | Placebo (Weekly infusion) | Epratuzumab 600 mg per week | Epratuzumab 1200 mg every other week |
|---|---------------------------|-----------------------------|--------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 45 / 263 (17.11%) | 50 / 264 (18.94%) | 45 / 261 (17.24%) |
| number of deaths (all causes) | 3 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Colon adenoma | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian adenoma | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 2 / 261 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 2 / 261 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Raynaud's phenomenon | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Temporal arteritis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy on contraceptive | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 263 (0.76%) | 3 / 264 (1.14%) | 4 / 261 (1.53%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 / 263 (0.00%) | 1 / 264 (0.38%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 4 / 264 (1.52%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Hypoxia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Lupus pleurisy | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lupus pneumonitis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| 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 alveolar haemorrhage | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 mass | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Generalised anxiety disorder | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| complications | | | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Post lumbar puncture syndrome | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Congenital, familial and genetic disorders | | | |
| Talipes | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 2 / 261 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 failure congestive | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Lupus myocarditis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Convulsion | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 263 (1.14%) | 1 / 264 (0.38%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lupus encephalitis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Migraine | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Nerve compression | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIIth nerve paralysis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vasculitis cerebral | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Noninfectious myelitis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Optic neuritis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 2 / 261 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 2 / 264 (0.76%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Antiphospholipid syndrome | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Necrotising retinitis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Cataract | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Retinal degeneration | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 263 (0.76%) | 1 / 264 (0.38%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Reflux gastritis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 1 / 264 (0.38%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Diverticulum intestinal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Enteritis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Hepatobiliary disorders | | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 3 / 263 (1.14%) | 0 / 264 (0.00%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Liver injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Cutaneous lupus erythematosus | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Purpura | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Rash | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angioedema | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 | | | |
| Lupus nephritis | | | |
| subjects affected / exposed | 2 / 263 (0.76%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 263 (0.76%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 7 / 263 (2.66%) | 6 / 264 (2.27%) | 6 / 261 (2.30%) |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 6 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Flank pain | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| 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 stiffness | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periarthritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovitis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Patellofemoral pain syndrome | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 263 (1.14%) | 4 / 264 (1.52%) | 2 / 261 (0.77%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 263 (0.76%) | 3 / 264 (1.14%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 2 / 261 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus chorioretinitis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Dermatitis infected | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 263 (1.14%) | 1 / 264 (0.38%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 1 / 264 (0.38%) | 0 / 261 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Infection | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 tuberculosis | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Sialoadenitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Skin bacterial infection | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Eye infection toxoplasmal | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Pyelonephritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 0 / 264 (0.00%) | 1 / 261 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 263 (0.00%) | 1 / 264 (0.38%) | 0 / 261 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 263 (0.38%) | 0 / 264 (0.00%) | 0 / 261 (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 |

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

| Non-serious adverse events | Placebo (Weekly infusion) | Epratuzumab 600 mg per week | Epratuzumab 1200 mg every other week |
|---|---------------------------|-----------------------------|--------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 159 / 263 (60.46%) | 163 / 264 (61.74%) | 154 / 261 (59.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 263 (4.56%) | 17 / 264 (6.44%) | 14 / 261 (5.36%) |
| occurrences (all) | 12 | 17 | 17 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 45 / 263 (17.11%) | 34 / 264 (12.88%) | 29 / 261 (11.11%) |
| occurrences (all) | 71 | 51 | 39 |

| | | | |
|--|-------------------------|------------------------|-------------------------|
| Dizziness subjects affected / exposed occurrences (all) | 13 / 263 (4.94%) 20 | 15 / 264 (5.68%) 17 | 10 / 261 (3.83%) 15 |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 14 / 263 (5.32%) 17 | 15 / 264 (5.68%) 18 | 15 / 261 (5.75%) 31 |
| Pyrexia subjects affected / exposed occurrences (all) | 17 / 263 (6.46%) 19 | 14 / 264 (5.30%) 19 | 8 / 261 (3.07%) 9 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 36 / 263 (13.69%) 52 | 25 / 264 (9.47%) 38 | 32 / 261 (12.26%) 41 |
| Diarrhoea subjects affected / exposed occurrences (all) | 20 / 263 (7.60%) 25 | 25 / 264 (9.47%) 41 | 15 / 261 (5.75%) 15 |
| Vomiting subjects affected / exposed occurrences (all) | 17 / 263 (6.46%) 20 | 16 / 264 (6.06%) 24 | 12 / 261 (4.60%) 14 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 12 / 263 (4.56%) 12 | 16 / 264 (6.06%) 19 | 12 / 261 (4.60%) 12 |
| Psychiatric disorders | | | |
| Depression subjects affected / exposed occurrences (all) | 15 / 263 (5.70%) 16 | 9 / 264 (3.41%) 12 | 10 / 261 (3.83%) 11 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 19 / 263 (7.22%) 20 | 14 / 264 (5.30%) 14 | 14 / 261 (5.36%) 16 |
| Systemic lupus erythematosus subjects affected / exposed occurrences (all) | 12 / 263 (4.56%) 13 | 12 / 264 (4.55%) 15 | 13 / 261 (4.98%) 15 |
| Arthralgia | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 14 / 263 (5.32%) 17 | 11 / 264 (4.17%) 11 | 10 / 261 (3.83%) 12 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 37 / 263 (14.07%) | 37 / 264 (14.02%) | 38 / 261 (14.56%) |
| occurrences (all) | 46 | 47 | 49 |
| Urinary tract infection | | | |
| subjects affected / exposed | 46 / 263 (17.49%) | 38 / 264 (14.39%) | 37 / 261 (14.18%) |
| occurrences (all) | 68 | 57 | 45 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 21 / 263 (7.98%) | 24 / 264 (9.09%) | 15 / 261 (5.75%) |
| occurrences (all) | 23 | 31 | 23 |
| Sinusitis | | | |
| subjects affected / exposed | 19 / 263 (7.22%) | 20 / 264 (7.58%) | 12 / 261 (4.60%) |
| occurrences (all) | 23 | 23 | 17 |
| Bronchitis | | | |
| subjects affected / exposed | 23 / 263 (8.75%) | 11 / 264 (4.17%) | 13 / 261 (4.98%) |
| occurrences (all) | 24 | 13 | 13 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 22 November 2011 | <p>The protocol was amended for the following reasons:</p> <ul style="list-style-type: none">- To change the name and contact information of the Clinical Trial Biostatistician and Study Physician- To add additional exploratory endpoints for assessment of the SF-36 and flares- To clarify the guidance for use of oral corticosteroids for the investigator- To add the sampling time points for overall B and T cell levels during the study and to add a body weight measurement at Week 48. These were inadvertently omitted from the original protocol- To modify Inclusion Criterion #5 for female subjects to allow abstinence alone and condoms/diaphragm use without adjunct spermicide- To modify Exclusion Criterion #15 to clarify that subjects who had previously received Emab treatment were excluded from participation in this study- To update the withdrawal criteria list: subjects who received a live vaccine during the study must have been withdrawn- To increase the Wash-Out Period for the prohibited concomitant treatment TACI-Ig (Atacicept®) from 3 months to 10 months based on recently reported data. The screening window had been increased from 2 days to 5 days, to allow the Screening Period to be extended after discussion with and approval of the medical monitor if it was in the best interest of the subject, and to allow rescreening of subjects on a case-by-case basis at the discretion of the medical monitor- To add additional details to the description of the SF-36 assessment- To include a list of Anticipated SAEs in compliance with the recent US FDA guidance on safety reporting requirements for studies conducted under an open Investigational New Drug Application (Food and Drug Administration [FDA], Guidance for Industry and Investigators, 2010)- To modify the definition of the Pharmacokinetic Set (PKS) to include the requirement of at least 1 Emab plasma concentration measurement <p>In addition, a few clarifications, inconsistencies, and typographical errors had been made/corrected within the protocol text</p> |
| 09 May 2014 | <p>The protocol was amended at the request of the German Regulatory Authority PEI to clarify details of the BILAG assessment, to introduce a list of adverse events (AEs) of special interest, and to clarify further actions after identification of an AE of special interest. Additional changes were as follows:</p> <ul style="list-style-type: none">- Updated study contact information- Updated SAE reporting information- Revised the exploratory endpoints for assessment of flares and for assessment of the SLICC/ACR Damage score- Added an additional safety variable (incidence of hospitalizations/emergency room [ER] visits)- Clarified the guidance for use of oral corticosteroids for the investigator to note that subjects with increases in oral corticosteroids above the allowed levels for an SLE-related indication are considered nonresponders- Corrected the visit numbers cited in Exclusion Criterion #14- Updated Steroid conversion table with additional corticosteroids- Updated the text "Preparation and administration of Emab and placebo" in order to clarify that it is recommended, but not mandatory, that subjects be premedicated before receiving an iv infusion- Updated the text "Handling and storage requirements" in order to clarify the process to follow in case of out-of-range temperatures- Updated the version number of the European Quality of Life-5 Dimensions questionnaire to European Quality of Life-5 Dimensions 3 level version- Modified the generalized estimating equation (GEE) sensitivity analysis in order to avoid known violations of the missing completely at random assumption, and to be consistent with the current SAP. The original plan for assessing the impact of missing data on the primary endpoint has not changed- Modified the text "Safety analyses" to state that infection TEAEs will be identified by including all events in the coded SOC "Infections and infestations" rather than via a review of all AE terms prior to study unblinding, as originally planned |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported