# Clinical trial results:
# A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) Administered Subcutaneously (SC) to Subjects with Systemic Lupus Erythematosus (SLE)

## Summary

| | |
|---|---|
| EudraCT number | 2011-003814-18 |
| Trial protocol | DE HU AT CZ SE BE PT ES DK GB BG IT PL |
| Global end of trial date | 01 October 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 20 May 2016 |
| First version publication date | 20 May 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 112341 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01484496 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1-866 4357343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1-866 4357343, |

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 | 12 February 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 01 October 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

- To evaluate the efficacy of belimumab administered SC in adult subjects with SLE.
- To evaluate the safety and tolerability of belimumab administered SC in adult subjects with SLE.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 16 November 2011 |
| 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: 20 |
| Country: Number of subjects enrolled | Brazil: 77 |
| Country: Number of subjects enrolled | Chile: 16 |
| Country: Number of subjects enrolled | Colombia: 41 |
| Country: Number of subjects enrolled | Croatia: 14 |
| Country: Number of subjects enrolled | Japan: 30 |
| Country: Number of subjects enrolled | Malaysia: 5 |
| Country: Number of subjects enrolled | Mexico: 18 |
| Country: Number of subjects enrolled | Philippines: 75 |
| Country: Number of subjects enrolled | Romania: 29 |
| Country: Number of subjects enrolled | Russian Federation: 19 |
| Country: Number of subjects enrolled | Serbia: 23 |
| Country: Number of subjects enrolled | Taiwan: 40 |
| Country: Number of subjects enrolled | Thailand: 22 |
| Country: Number of subjects enrolled | Ukraine: 27 |
| Country: Number of subjects enrolled | United States: 237 |
| Country: Number of subjects enrolled | Poland: 36 |
| Country: Number of subjects enrolled | Portugal: 15 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Austria: 7 |

| | |
|---|---|
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Bulgaria: 18 |
| Country: Number of subjects enrolled | Czech Republic: 13 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Hungary: 9 |
| Country: Number of subjects enrolled | Italy: 6 |
| Worldwide total number of subjects | 836 |
| EEA total number of subjects | 186 |

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) | 817 |
| From 65 to 84 years | 19 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants (par.) with active systemic lupus erythematosus (SLE) and who were on appropriate stable standard SLE therapy for a period of at least 30 days prior to Day 0 before entering the study were eligible for participation in the study.

### Pre-assignment

Screening details:

A total of 1427 par. were screened, out of these 588 par. were screen failures and 839 par. were randomized, of which 836 par. received at least one dose of study treatment. Participants who successfully completed the initial 52-week Double-blind Phase had a choice to enter into a 6-month Open-label Extension Phase of this study.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo SC |

Arm description:

Participants received placebo administered subcutaneously (SC) once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period.

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

Dosage and administration details:

Placebo will be supplied as single-use prefilled syringes; Participants will be dosed with placebo on Day 0 and then weekly through 51 weeks of treatment.

| | |
|---|---|
| **Arm title** | Belimumab 200 mg SC |

Arm description:

Participants received belimumab 200 milligrams (mg) administered SC once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period.

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

Dosage and administration details:

Belimumab 200 mg for SC injection will be supplied as single-use prefilled syringes; Participants will be dosed with study agent on Day 0 and then weekly through 51 weeks of treatment.

| **Number of subjects in period 1** | Placebo SC | Belimumab 200 mg SC |
|---|---|---|
| Started | 280 | 556 |
| Completed | 214 | 463 |
| Not completed | 66 | 93 |
| Adverse event, serious fatal | 2 | 2 |
| Consent withdrawn by subject | 15 | 12 |
| Lack of Compliance | 2 | 1 |
| Physician decision | 5 | 1 |
| Unable to Visit Site | - | 2 |
| Adverse event, non-fatal | 23 | 38 |
| Treatment Failure | 3 | 6 |
| Lost to follow-up | 2 | 6 |
| Positive Pregnancy | 1 | 6 |
| Lack of efficacy | 10 | 15 |
| Protocol deviation | 3 | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo SC |
| Reporting group description: | |
| Participants received placebo administered subcutaneously (SC) once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period. | |
| Reporting group title | Belimumab 200 mg SC |
| Reporting group description: | |
| Participants received belimumab 200 milligrams (mg) administered SC once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period. | |

| Reporting group values | Placebo SC | Belimumab 200 mg SC | Total |
|---|---|---|---|
| Number of subjects | 280 | 556 | 836 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.6 | 38.1 | |
| standard deviation | ± 12.61 | ± 12.1 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 268 | 521 | 789 |
| Male | 12 | 35 | 47 |
| Race | | | |
| Units: Subjects | | | |
| White/Caucasian/European Heritage | 160 | 326 | 486 |
| Middle East/North African Heritage | 6 | 10 | 16 |
| Central Asian Heritage | 0 | 2 | 2 |
| East Asian Heritage | 15 | 29 | 44 |
| Japanese Heritage | 16 | 13 | 29 |
| South Asian Heritage | 0 | 2 | 2 |
| Southeast Asian Heritage | 32 | 73 | 105 |
| African American/African Heritage | 30 | 56 | 86 |
| American Indian or Alaska Native | 21 | 43 | 64 |
| Native Hawaiian or Other Pacific Islander | 0 | 2 | 2 |

## End points

### End points reporting groups

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

Reporting group description:

Participants received placebo administered subcutaneously (SC) once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period.

| | |
|---|---|
| Reporting group title | Belimumab 200 mg SC |

Reporting group description:

Participants received belimumab 200 milligrams (mg) administered SC once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period.

### Primary: Percentage of participants achieving a SRI response at Week 52

| | |
|---|---|
| End point title | Percentage of participants achieving a SRI response at Week 52 |

End point description:

Systemic lupus erythematosus responder index (SRI) response is defined as >=4 point reduction from Baseline in safety of estrogen in lupus national assessment (SELENA) systemic lupus erythematosus disease activity index (SLEDAI) score, no worsening (increase of <0.30 points from Baseline) in physician's global assessment (PGA) and no new british isles lupus assessment group of SLE clinics (BILAG) A organ domain score or 2 new BILAG B organ domain scores compared with Baseline. Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, Baseline SELENA SLEDAI score (<=9 vs. >=10), Baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other). Intention-To-Treat (ITT) Population: comprised of all participants who were randomized and treated with at least one dose of study treatment.

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

End point timeframe:

Week 52

| End point values | Placebo SC | Belimumab 200 mg SC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 279[1] | 554[2] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 48.4 | 61.4 | | |

Notes:

[1] - ITT population. Three par. did not have a Baseline PGA assessment; therefore, were not included.

[2] - ITT population. Three par. did not have a Baseline PGA assessment; therefore, were not included.

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 1 |
| Comparison groups | Placebo SC v Belimumab 200 mg SC |

| | |
|---|---|
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.25 |
| upper limit | 2.25 |

## Secondary: Time to first severe flare (as measured by the modified SLE Flare Index)

| | |
|---|---|
| End point title | Time to first severe flare (as measured by the modified SLE Flare Index) |

End point description:

Time to first severe SLE flare is defined as the number of days from treatment start date until the participant met an event (event date – treatment start date +1). Analyses of severe SLE flare was performed on modified SELENA SLEDAI SLE flare index that excludes severe flares that were triggered only by an increase in SELENA SLEDAI score to >12 (since this may only represent a modest increase in disease activity). Only post-Baseline severe flares were considered. Analysis was performed using a Cox proportional hazards model adjusting for Baseline SELENA SLEDAI score (<=9 vs. >=10), Baseline complement levels, (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other).

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

End point timeframe:

Baseline to Week 52

| End point values | Placebo SC | Belimumab 200 mg SC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 280[3] | 556[4] | | |
| Units: Percentage of par. with a severe flare | | | | |
| number (not applicable) | 18.2 | 10.6 | | |

Notes:

[3] - ITT Population

[4] - ITT Population

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Belimumab 200 mg SC v Placebo SC |

| | |
|---|---|
| Number of subjects included in analysis | 836 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 0.74 |

## Secondary: Percentage of participants whose average prednisone dose had been reduced by >=25% from Baseline to <=7.5 mg/day during weeks 40 through 52 in participants receiving greater than 7.5 mg/day at Baseline

| | |
|---|---|
| End point title | Percentage of participants whose average prednisone dose had been reduced by >=25% from Baseline to <=7.5 mg/day during weeks 40 through 52 in participants receiving greater than 7.5 mg/day at Baseline |

End point description:

For the analysis of steroid use, all steroid dosages were converted to a prednisone equivalent in milligrams. The average daily prednisone dose was calculated taking into account all steroids taken intravenously, intramuscularly, SC, intradermally and orally for both SLE and non-SLE reasons. A responder was defined as having a prednisone reduction by >=25% from Baseline to <=7.5 mg/day during Weeks 40 through 52. At Baseline, the average daily prednisone dose was the sum of all prednisone doses over 7 consecutive days up to, but not including Day 0, divided by 7. For this analysis, the average prednisone dose was the total prednisone dose during weeks 40 through 52 divided by the number of days during Weeks 40 through 52. Analysis was performed using a logistic regression model with covariates treatment group, Baseline prednisone dose, Baseline SELENA SLEDAI score, (<=9 vs. >=10), Baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other).

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

End point timeframe:

Baseline, Weeks 40 through Week 52

| **End point values** | Placebo SC | Belimumab 200 mg SC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168[5] | 335[6] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 11.9 | 18.2 | | |

Notes:

[5] - ITT population. Only participants with Baseline prednisone dose >7.5 mg/day were included.

[6] - ITT population. Only participants with Baseline prednisone dose >7.5 mg/day were included.

### Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|
| Comparison groups | Placebo SC v Belimumab 200 mg SC |

| | |
|---|---|
| Number of subjects included in analysis | 503 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0732 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 2.84 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study agent administration through the Week 52 visit (or Exit visit for those participants who withdrew during double-blind treatment).

Adverse event reporting additional description:

AEs and SAEs were collected in participants of ITT population, comprised of participants who were randomized and treated with at least one dose of study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

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

Reporting group description:

Participants received placebo administered SC once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period.

| | |
|---|---|
| Reporting group title | Belimumab 200 mg SC |

Reporting group description:

Participants received belimumab 200 mg administered SC once weekly through 51 weeks of the treatment period. Participants continued with the stable standard therapy they were receiving during the Screening Period.

| Serious adverse events | Placebo SC | Belimumab 200 mg SC | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 44 / 280 (15.71%) | 60 / 556 (10.79%) | |
| number of deaths (all causes) | 2 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraductal proliferative breast lesion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipoma of breast | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid neoplasm | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lupus vasculitis | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |

| | | | |
|---|---|---|---|
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 556 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystocele | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine prolapse | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alveolitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Procedural vomiting | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropsychiatric lupus | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lupus encephalitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Exfoliation syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Systemic lupus erythematosus rash | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Drug eruption | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 4 / 556 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lupus nephritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritic syndrome | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| SLE arthritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Costochondritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyarthritis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 3 / 556 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 4 / 556 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 3 / 556 (0.54%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 556 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Amoebic dysentery | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 556 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Corynebacterium sepsis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| External ear cellulitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gasteroenteritis viral | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis bacterial | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus bronchitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salmonellosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis of central nervous system | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 556 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 556 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo SC | Belimumab 200 mg SC | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 230 / 280 (82.14%) | 440 / 556 (79.14%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 25 / 556 (4.50%) | |
| occurrences (all) | 21 | 26 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 25 / 280 (8.93%) | 57 / 556 (10.25%) | |
| occurrences (all) | 51 | 83 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 22 / 280 (7.86%) | 38 / 556 (6.83%) | |
| occurrences (all) | 30 | 74 | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 27 / 556 (4.86%) | |
| occurrences (all) | 17 | 38 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 19 / 280 (6.79%) | 22 / 556 (3.96%) | |
| occurrences (all) | 20 | 26 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 20 / 280 (7.14%) | 18 / 556 (3.24%) | |
| occurrences (all) | 21 | 20 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 15 / 280 (5.36%) | 28 / 556 (5.04%) | |
| occurrences (all) | 16 | 31 | |
| Arthralgia | | | |
| subjects affected / exposed | 11 / 280 (3.93%) | 31 / 556 (5.58%) | |
| occurrences (all) | 11 | 42 | |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 24 / 280 (8.57%) | 48 / 556 (8.63%) | |
| occurrences (all) | 32 | 77 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 22 / 280 (7.86%) | 38 / 556 (6.83%) | |
| occurrences (all) | 30 | 56 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 18 / 280 (6.43%) | 41 / 556 (7.37%) | |
| occurrences (all) | 22 | 44 | |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 30 / 556 (5.40%) | |
| occurrences (all) | 15 | 33 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 August 2011 | Amendment 01 applied to all sites. The composition of the DMC was revised to indicate that at least 3 physicians were included without specifying their specialty areas in order to allow flexibility when constituting the DMC for this study; frequency of prothrombin time (PT) and partial thromboplastin time (PTT) assessments were reduced; and assessment of C-reactive protein (CRP) was removed. |
| 04 October 2011 | Amendment 02 applied to all sites. The amount of time for subjects to be monitored following self-administration of study agent on the first (Day 0) and second (Day 7) injections was increased from 1 to 3 hours in the treatment and 6-month open label extension phase based on reports of serious hypersensitivity reactions occurring outside of the 2 hour window. The efficacy analysis sections were updated to clarify that if the Day 364 (Week 52) visit is missing, data collected at a visit within 28 days of the Day 364 (Week 52) visit would be used for analysis of the primary and major secondary efficacy endpoints. |
| 17 November 2011 | Amendment 03 applied to all sites. The DMC monitoring schedule after the first meeting was changed from approximately every 4 months to approximately every 6 months to align the schedule with other trials of belimumab in SLE. The protocol was also modified to delete the long-term extension phase after the 6-month open-label extension. Provision of continuing belimumab treatment to subjects who were benefitting and resided in countries where belimumab was not commercially available was achieved in a separate continuation protocol, in which subjects received IV belimumab every 4 weeks until belimumab was commercially available. |
| 21 February 2012 | Amendment 04 applied to all sites. Inclusion criteria #6 was amended to recommend that women receiving mycophenolate who relied on oral contraceptives for birth control should employ an additional method (e.g., barrier method). This change was made because mycophenolate mofetil (MMF) and other forms of mycophenolate can affect the metabolism of oral contraceptives and may reduce their effectiveness [CellCept package insert, 2015]. Language was added as a safety precaution to clarify the risk of hypersensitivity reactions, to emphasize patient education about the signs and symptoms of hypersensitivity reactions, and to recommend consideration of an extended period of monitoring (greater than the protocol-specified 3 hours after the first 2 injections) if symptoms of acute hypersensitivity were apparent. The protocol was also modified to indicate that from the time a subject consented to participate in the study and prior to treatment, any SAEs deemed to be related to participation in the study were also collected. |
| 06 August 2013 | This local amendment applied to sites in the US, UK, Spain, Portugal, Sweden and Denmark. Exclusion criteria 1 and 2 were modified so that treatment with B cell targeted therapy 1 year or more ago was permitted. Previous treatment with belimumab was still not allowed. Literature evidence supported that the majority of patients have largely recovered from immunosuppressive effects of B cell depletion within 1 year after treatment with B cell targeted therapy [Rituxan package insert, 2014]. Also, there were supplementary clinical and laboratory exclusion criteria already in place would that identify and exclude patients with residual immune suppression. Countries that participated in this local amendment were selected based on estimates of subjects with exposure of at least 1 year to B cell targeted therapy. |

| | |
|---|---|
| 12 June 2014 | Amendment 05 applied to all sites. The protocol was modified to clarify the timing of the Exit visit and the requirements for the 8-week follow-up visit and the target window of the first dose of IV belimumab following last dose of SC belimumab was added. Progressive multifocal leukoencephalopathy (PML) text was updated based on new information. PK sampling schedule after Day 168 was modified to allow discontinuation of PK sample collection. PK sections were modified to indicate a subset of samples may be used to characterize serum belimumab biochemical attributes and to describe the methodology to be used for this purpose. In subjects who had a positive antibody response at the 8-week follow-up, timing of additional sample collection was made more flexible. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported