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	2010-018563-41
Trial protocol	BE ES DE CZ GB BG LT EE IT
Global end of trial date	15 May 2015

Results information

Result version number	v1
This version publication date	29 May 2016
First version publication date	29 May 2016

Trial information

Trial identification

Sponsor protocol code	SL0009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01262365
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	24 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	15 May 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 moderate to severe general Systemic Lupus Erythematosus (SLE) despite standard of care treatments (i.e., corticosteroids, and potentially antimalarials and immunosuppressants) continued from Baseline.

Protection of trial subjects:

Patients were pre-medicated prior to infusion of 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 ≤7.5mg/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, dapsone, 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	09 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	Australia: 43
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Brazil: 50

Country: Number of subjects enrolled	Bulgaria: 59
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	India: 9
Country: Number of subjects enrolled	Israel: 38
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Lithuania: 24
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 293
Worldwide total number of subjects	793
EEA total number of subjects	287

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)	770
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in December 2010 and concluded in May 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: -

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: -

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: -

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	266	262	265
Completed	176	181	171
Not completed	90	81	94
Consent withdrawn by subject	17	22	22
AE(s), serious non-fatal	13	10	5
AE(s), serious fatal	1	2	1
AE(s), non-serious non-fatal	12	5	5
other	5	3	6
Lost to follow-up	3	7	6
Lack of efficacy	35	30	47
Protocol deviation	3	1	1
SAE(s), non-fatal and AE(s), non-serious non-fatal	1	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	259	264
Age Categorical Units: Subjects			
<=18 years	2	0	0
Adults (18-64 years)	250	254	257
>=65 years	11	5	7
Age Continuous Units: years			
arithmetic mean	41.4	42.5	42.3
standard deviation	± 12.6	± 11.8	± 11.4
Gender Categorical Units: Subjects			
Male	13	16	22
Female	250	243	242

Reporting group values	Placebo (Weekly infusion) FAS	Epratuzumab 1200 mg every other week (FAS)	Epratuzumab 600 mg per week (FAS)
Number of subjects	249	244	248
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: -	
Reporting group title	Epratuzumab 1200 mg every other week (RS)
Reporting group description: -	
Reporting group title	Epratuzumab 600 mg per week (RS)
Reporting group description: -	
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	249	244	248	
Units: percentage of				
number (not applicable)				
Responder	34.1	39.8	37.5	

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	493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.307
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.888
upper limit	1.923

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	497
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.442
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.714

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	249	244	248	
Units: percentage of				
number (not applicable)				
Responder	33.7	43	39.1	

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	249	244	248	
Units: percentage of				
number (not applicable)				
Responder	31.3	42.2	39.9	

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	249	244	248	
Units: percentage of				
number (not applicable)				
Responder	33.3	41.8	35.1	

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:

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	249	244	248	
Units: percentage of				
number (not applicable)				
Dose decreased by >50%	9.2	8.2	6.9	
Dose decreased >0% to <=50%	10.8	16.4	14.9	
No change in dose	52.2	50	50.8	

Dose increased or missing data	27.7	25.4	27.4	

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:

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	249	244	248	
Units: percentage of				
number (not applicable)				
Dose decreased by >50%	14.1	11.9	10.1	
Dose decreased >0% to <=50%	10.4	14.3	12.5	
No chnage in dose	38.6	37.7	37.9	
Dose increased or missing data	36.9	36.1	37.9	

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 December in 2010 and concluded in May 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 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

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

Serious adverse events	Placebo (Weekly infusion)	Epratuzumab 1200 mg every other week	Epratuzumab 600 mg per week
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 263 (18.25%)	44 / 259 (16.99%)	45 / 264 (17.05%)
number of deaths (all causes)	1	2	2
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	1 / 264 (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
Colon adenoma			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	2 / 264 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Arteriosclerosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Jugular vein thrombosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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 vasculitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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 / 259 (0.00%)	1 / 264 (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%)	0 / 259 (0.00%)	2 / 264 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Pyrexia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Non-cardiac chest pain			
subjects affected / exposed	2 / 263 (0.76%)	0 / 259 (0.00%)	0 / 264 (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
Serositis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serum sickness			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Reproductive system and breast disorders			
Breast ulceration			

subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Endometriosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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 cyst ruptured			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	0 / 264 (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
Vaginal haemorrhage			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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%)	0 / 259 (0.00%)	2 / 264 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 263 (0.00%)	2 / 259 (0.77%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Asthma			

subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Pleural effusion			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Respiratory failure			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Psychiatric disorders			
Delirium tremens			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Suicidal ideation			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Bipolar I disorder			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Depression			

subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Weight decreased			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Femoral neck fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Fibula fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Foot fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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			
Arteriovenous malformation			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular arteriovenous malformation			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Pericardial effusion			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis lupus			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	0 / 264 (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
Pericarditis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Nervous system disorders			
Convulsion			

subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery thrombosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Ischaemic stroke			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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 encephalitis			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Hemiparesis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Hypoaesthesia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Mononeuropathy multiplex			

subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 263 (0.00%)	2 / 259 (0.77%)	2 / 264 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Pancytopenia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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 / 259 (0.00%)	1 / 264 (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
Splenomegaly			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	3 / 264 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Impaired gastric emptying			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Nausea			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Pancreatitis acute			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Vomiting			

subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Abdominal discomfort			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Bezoar			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Diarrhoea			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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			
Cholelithiasis			
subjects affected / exposed	1 / 263 (0.38%)	2 / 259 (0.77%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lupus hepatitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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%)	0 / 259 (0.00%)	1 / 264 (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
Hidradenitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Swelling face			

subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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 and urinary disorders			
Lupus nephritis			
subjects affected / exposed	2 / 263 (0.76%)	2 / 259 (0.77%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	1 / 263 (0.38%)	2 / 259 (0.77%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	1 / 264 (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 / 1
Nephrolithiasis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Proteinuria			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Renal failure acute			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Renal impairment			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Urinary retention			

subjects affected / exposed	2 / 263 (0.76%)	0 / 259 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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 and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	3 / 263 (1.14%)	5 / 259 (1.93%)	3 / 264 (1.14%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Haemarthrosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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 chest pain			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Osteonecrosis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Osteoporotic fracture			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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

Back pain			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Cervical spinal stenosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 263 (0.00%)	3 / 259 (1.16%)	3 / 264 (1.14%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	0 / 263 (0.00%)	3 / 259 (1.16%)	2 / 264 (0.76%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	4 / 264 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 263 (1.52%)	1 / 259 (0.39%)	2 / 264 (0.76%)
occurrences causally related to treatment / all	3 / 4	0 / 1	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	1 / 264 (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
Abscess neck			

subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Atypical pneumonia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Bronchopneumonia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Erysipelas			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	1 / 264 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Herpes zoster			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Bacterial pyelonephritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Herpes zoster meningitis			

subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Influenza			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Localised infection			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Lymphangitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Myringitis bullous			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Pelvic inflammatory disease			
subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	1 / 263 (0.38%)	1 / 259 (0.39%)	0 / 264 (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
Pyomyositis			

subjects affected / exposed	0 / 263 (0.00%)	1 / 259 (0.39%)	0 / 264 (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
Septic shock			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Bronchitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Diarrhoea infectious			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Pneumococcal sepsis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Viral infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 259 (0.00%)	0 / 264 (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
Appendicitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Hypophosphataemia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Obesity			
subjects affected / exposed	0 / 263 (0.00%)	0 / 259 (0.00%)	1 / 264 (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
Hyperglycaemia			
subjects affected / exposed	2 / 263 (0.76%)	0 / 259 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	1 / 2	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 1200 mg every other week	Epratuzumab 600 mg per week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	222 / 263 (84.41%)	228 / 259 (88.03%)	211 / 264 (79.92%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 263 (4.18%)	20 / 259 (7.72%)	14 / 264 (5.30%)
occurrences (all)	12	21	16
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 263 (11.03%)	34 / 259 (13.13%)	38 / 264 (14.39%)
occurrences (all)	38	42	58
Dizziness			
subjects affected / exposed	11 / 263 (4.18%)	9 / 259 (3.47%)	16 / 264 (6.06%)
occurrences (all)	11	10	18
Migraine			

subjects affected / exposed	3 / 263 (1.14%)	16 / 259 (6.18%)	7 / 264 (2.65%)
occurrences (all)	4	19	8
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 263 (3.80%)	17 / 259 (6.56%)	12 / 264 (4.55%)
occurrences (all)	10	20	17
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	23 / 263 (8.75%)	30 / 259 (11.58%)	39 / 264 (14.77%)
occurrences (all)	28	44	50
Diarrhoea			
subjects affected / exposed	18 / 263 (6.84%)	21 / 259 (8.11%)	19 / 264 (7.20%)
occurrences (all)	20	24	28
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 263 (4.56%)	13 / 259 (5.02%)	12 / 264 (4.55%)
occurrences (all)	16	14	12
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 263 (1.90%)	14 / 259 (5.41%)	8 / 264 (3.03%)
occurrences (all)	5	16	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 263 (5.32%)	20 / 259 (7.72%)	14 / 264 (5.30%)
occurrences (all)	21	28	24
Back pain			
subjects affected / exposed	11 / 263 (4.18%)	19 / 259 (7.34%)	15 / 264 (5.68%)
occurrences (all)	15	20	17
Pain in extremity			
subjects affected / exposed	11 / 263 (4.18%)	14 / 259 (5.41%)	9 / 264 (3.41%)
occurrences (all)	13	18	9
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	30 / 263 (11.41%)	32 / 259 (12.36%)	32 / 264 (12.12%)
occurrences (all)	36	38	38
Urinary tract infection			

subjects affected / exposed	30 / 263 (11.41%)	25 / 259 (9.65%)	30 / 264 (11.36%)
occurrences (all)	41	29	45
Nasopharyngitis			
subjects affected / exposed	21 / 263 (7.98%)	20 / 259 (7.72%)	22 / 264 (8.33%)
occurrences (all)	26	21	29
Sinusitis			
subjects affected / exposed	13 / 263 (4.94%)	24 / 259 (9.27%)	15 / 264 (5.68%)
occurrences (all)	14	24	17
Bronchitis			
subjects affected / exposed	21 / 263 (7.98%)	12 / 259 (4.63%)	15 / 264 (5.68%)
occurrences (all)	24	14	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2011	The protocol was amended for the following reasons: - 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 In addition, a few clarifications, inconsistencies, and typographical errors had been made/corrected within the protocol text
09 May 2014	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: - 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