Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis

Summary

EudraCT number	2011-004570-28
Trial protocol	HU DE GB BE ES CZ NL FR
Global end of trial date	12 March 2020

Results information

Result version number	v1
This version publication date	27 June 2020
First version publication date	27 June 2020

Trial information

Trial identification

Sponsor protocol code	BEL114054

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	Interim
Date of interim/final analysis	10 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2019
Global end of trial reached?	Yes
Global end of trial date	12 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy, safety, and tolerability of belimumab in adult patients with active lupus nephritis.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 2012
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: 34
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Brazil: 32
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	China: 79
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Korea, Republic of: 43
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Philippines: 45
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Thailand: 25
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 76

Worldwide total number of subjects	448
EEA total number of subjects	77

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)	446
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled study that evaluated safety and efficacy of intravenous (IV) belimumab 10 milligrams per kilogram (mg/kg) plus standard of care (SoC) compared to placebo plus SoC in adult participants with active lupus nephritis.The study was conducted in 21 countries.

Pre-assignment

Screening details:

A total of 797 participants were screened for the study of which 448 participants were enrolled. The results presented are for the primary analysis (double blind treatment period)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were randomized to receive matching placebo IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus Cyclophosphamide [CYC] versus [vs.] HDCS plus Mycophenolate Mofetil [MMF]) and race.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered with Placebo intravenously (IV) along with standard of care (SoC) on Days 0, 14, 28, and then every 28 days thereafter through Week 100, with a final evaluation at Week 104.

Arm title	Belimumab 10 mg/kg

Arm description:

Participants were randomized to receive Belimumab 10 mg/kg IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (HDCS plus CYC vs. HDCS plus MMF) and race.

Arm type	Experimental
Investigational medicinal product name	Belimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered with Belimumab 10 milligrams per kilograms (mg/kg) IV along with SoC on Days 0, 14, 28, and then every 28 days thereafter through Week 100, with a final evaluation at Week 104.

Number of subjects in period 1	Placebo	Belimumab 10 mg/kg
Started	224	224
Completed	170	186
Not completed	54	38
Adverse event, serious fatal	5	6
Consent withdrawn by subject	26	19
Physician decision	11	5
Adverse event, non-fatal	5	1
Lost to follow-up	5	4
Lack of efficacy	2	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive matching placebo IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus Cyclophosphamide [CYC] versus [vs.] HDCS plus Mycophenolate Mofetil [MMF]) and race.	
Reporting group title	Belimumab 10 mg/kg
Reporting group description:	
Participants were randomized to receive Belimumab 10 mg/kg IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (HDCS plus CYC vs. HDCS plus MMF) and race.	

Reporting group values	Placebo	Belimumab 10 mg/kg	Total
Number of subjects	224	224	448
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	222	224	446
From 65-84 years	2	0	2
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	33.0	33.7	
standard deviation	± 10.64	± 10.73	-
Sex: Female, Male Units: Participants			
Female	196	198	394
Male	28	26	54
Race/Ethnicity, Customized Units: Subjects			
American Indian (AI) or Alaska Native (AN)	6	4	10
Asian-Central/South Asian Heritage (H)	2	3	5
Asian-Japanese/East Asian/Southeast Asian H	107	112	219
Mixed Asian	1	0	1
Black or African American (AA)	31	30	61
White/Caucasian/European H	71	72	143

White/Caucasian/Arabic/North African H	4	1	5
Multiple-AA/African H and AI or AN and White	1	1	2
Multiple-Asian and White	1	1	2

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were randomized to receive matching placebo IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus Cyclophosphamide [CYC] versus [vs.] HDCS plus Mycophenolate Mofetil [MMF]) and race.

Reporting group title	Belimumab 10 mg/kg

Reporting group description:

Participants were randomized to receive Belimumab 10 mg/kg IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (HDCS plus CYC vs. HDCS plus MMF) and race.

Primary: Percentage of participants with primary efficacy renal response (PERR) at Week 104

End point title	Percentage of participants with primary efficacy renal response (PERR) at Week 104

End point description:

PERR is defined as urinary protein creatinine ratio <=0.7, estimated glomerular filtration rate (eGFR) was not more than 20 percent (%) below the pre-flare value or >=60 milliliters per minute per 1.73 square meter (mL/min/1.73m^2) and was not a treatment failure. Analysis was performed using a logistic regression model for the comparison between Belimumab and Placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), Baseline urine protein-creatinine ratio (uPCR) and Baseline eGFR. Modified Intent-to-treat (MITT) Population consisted of all randomized participants who received at least one dose of study treatment and were not in one of 2 sites excluded due to GCP compliance. Percentage of participants with PERR at Week 104 has been presented.

End point type	Primary

End point timeframe:

Week 104

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[1]	223[2]		
Units: Percentage of participants				
number (not applicable)	32.3	43.0		

Notes:

[1] - mITT Population

[2] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Belimumab 10 mg/kg v Placebo

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0311 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.32

Notes:

[3] - Treatment comparison between Belimumab 10 mg/kg and placebo using odds ratio and its corresponding 95% confidence interval has been presented.

[4] - P-value was calculated using logistic regression model. Test 1 of 5 in a step-down sequential testing procedure.

Secondary: Percentage of participants with complete renal response (CRR) at Week 104

End point title	Percentage of participants with complete renal response (CRR) at Week 104

End point description:

CRR is defined as urinary protein creatinine ratio <0.5, eGRF was not more than 10% below the pre-flare value or >=90 mL/min/1.73m^2 and was not a treatment failure. Analysis was performed using a logistic regression model for the comparison between Belimumab and Placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), Baseline uPCR and Baseline eGFR. Percentage of participants with CRR at Week 104 has been presented.

End point type	Secondary

End point timeframe:

Week 104

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[5]	223[6]		
Units: Percentage of participants				
number (not applicable)	19.7	30.0		

Notes:

[5] - mITT Population.

[6] - mITT Population.

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Belimumab 10 mg/kg

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0167 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	2.74

Notes:

[7] - Treatment comparison between Belimumab 10 mg/kg and placebo using odds ratio and its corresponding 95% confidence interval has been presented.
[8] - P-value was calculated using logistic regression model. Test 2 of 5 in a step-down sequential testing procedure.

Secondary: Percentage of participants with PERR at Week 52

End point title	Percentage of participants with PERR at Week 52

End point description:

PERR is defined as urinary protein creatinine ratio <=0.7, eGRF was not more than 20% below the pre-flare value or >=60 mL/min/1.73m^2 and was not a treatment failure. Analysis was performed using a logistic regression model for the comparison between Belimumab and Placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), uPCR and Baseline eGFR. Percentage of participants with PERR at Week 52 has been presented.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[9]	223[10]		
Units: Percentage of participants				
number (not applicable)	35.4	46.6		

Notes:

[9] - mITT Population

[10] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Belimumab 10 mg/kg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0245 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.38

Notes:

[11] - Treatment comparison between Belimumab 10 mg/kg and placebo using odds ratio and its corresponding 95% confidence interval has been presented.
[12] - P-value was calculated using logistic regression model. Test 3 of 5 in a step-down sequential testing procedure.

Secondary: Number of participants with time to death or renal related event

End point title	Number of participants with time to death or renal related event

End point description:

Events are defined as the first event experienced among the following: death, progression to end stage renal disease, doubling of serum creatinine from Baseline, renal worsening or renal-related treatment failure. Participants who discontinued randomized treatment, withdrawn from the study, or are lost to follow-up were censored on the date of the event. Participants who completed the 104-week treatment period were censored at the Week 104 visit. Time to event is defined as event date minus treatment start date plus one. Analysis was performed using Cox proportional hazards model for the comparison between Belimumab and Placebo adjusting for induction regimen, race, baseline uPCR, and Baseline eGFR. Number of participants with time to death or renal related event up to Week 104 has been presented.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[13]	223[14]		
Units: Participants	63	35		

Notes:

[13] - mITT Population

[14] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Belimumab 10 mg/kg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0014 [16]
Method	Cox proportional hazards model
Parameter estimate	Cox proportional hazard
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.77

Notes:

[15] - Treatment comparison between Belimumab 10 mg/kg and placebo using Cox proportional hazards ratio and its corresponding 95% confidence interval has been presented.
[16] - P-value was calculated using Cox proportional hazards model. Test 4 of 5 in a step-down sequential testing procedure

Secondary: Percentage of participants with ordinal renal response (ORR) at Week 104

End point title	Percentage of participants with ordinal renal response (ORR) at Week 104

End point description:

ORR is defined with respect to reproducible responses that included CRR, partial RR (PRR) and non responder. CRR is reported when uPCR was <0.5, eGFR was not more than 10% below pre-flare GFR or within normal range and not a treatment failure. PRR is >=50% decrease from Baseline in uPCR and one of the following: value <1 if Baseline <=3, or value <3 if the Baseline was >3, eGFR not more than 10% below Baseline GFR or within normal range and not a treatment failure and not a CRR. Non responder is reported when neither CRR nor PRR criteria was met. Percentage of participants reporting CRR, PRR and non responders at Week 104 has been presented.

End point type	Secondary

End point timeframe:

Week 104

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[17]	223[18]		
Units: Percentage of participants				
number (not applicable)				
CRR	19.7	30.0		
PRR	17.0	17.5		
Non responder	63.2	52.5		

Notes:

[17] - mITT Population

[18] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Belimumab 10 mg/kg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0096 [19]
Method	Rank ANCOVA

Notes:

[19] - P-value is rank analysis of covariance model comparing Belimumab and Placebo with covariates for treatment group, induction regimen(CYC vs MMF),race(Black vs Non-black), Baseline uPCR, and eGFR. Test 5 of 5 in step-down sequential testing procedure.

Other pre-specified: Number of participants reporting on-treatment adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants reporting on-treatment adverse events (AEs) and serious adverse events (SAEs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any dose: resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinemia were categorized as SAE. Number of participants with on-treatment AE/ SAE has been reported. Safety Population comprises of all randomized participants who received at least one dose of study treatment.

End point type	Other pre-specified

End point timeframe:

Up to Week 104

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[20]	224[21]		
Units: Participants				
Any AE	211	214		
Any SAE	67	58		

Notes:

[20] - Safety Population.

[21] - Safety Population.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of participants reporting on-treatment adverse events of special interest (AESI)

End point title	Number of participants reporting on-treatment adverse events of special interest (AESI)

End point description:

An AESI is one of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by investigator to sponsor can be appropriate. A summary of protocol defined AESIs include malignant neoplasms including and excluding non-melanoma skin cancer (NMSC), post-infusion systemic reactions (PISR), all infections of special interest (opportunistic infections [OI], Herpes Zoster [HZ], tuberculosis [TB], and sepsis), depression (including mood disorders and anxiety)/suicide/self-injury and deaths (On-treatment AE with death occurring anytime). Number of participants reporting on-treatment AESI has been presented.

End point type	Other pre-specified

End point timeframe:

Up to Week 104

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[22]	224[23]		
Units: Participants				
Malignancies excluding NMSC	0	2		
Malignancies including NMSC	0	3		

PISR	29	26		
All infections of special interest	34	30		
Depression/suicide/self-injury	16	11		
Deaths	3	4		

Notes:

[22] - Safety Population.

[23] - Safety Population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were reported from start of treatment until Week 104. All AEs are included regardless of time since last investigational product (IP) treatment.

Adverse event reporting additional description:

AEs and SAEs were collected for Safety Population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Belimumab 10 mg/kg

Reporting group description:

Participants were randomized to receive Belimumab 10 mg/kg IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (HDCS plus CYC vs. HDCS plus MMF) and race.

Reporting group title	Placebo

Reporting group description:

Participants were randomized to receive matching placebo IV plus SoC on Days 0 (Baseline), 14, 28 and then every 28 days thereafter through 100 Weeks with a final evaluation for the double-blind treatment period at Week 104. The randomization was stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus Cyclophosphamide [CYC] versus [vs.] HDCS plus Mycophenolate Mofetil [MMF]) and race.

Serious adverse events	Belimumab 10 mg/kg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 224 (29.02%)	78 / 224 (34.82%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thymoma			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 224 (0.89%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypotension			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal death			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prolonged labour			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 224 (0.89%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 224 (0.89%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 224 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Serositis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
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	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppression			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Organizing pneumonia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood immunoglobulin G decreased			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal biophysical profile score equivocal			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	2 / 224 (0.89%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain herniation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Contusion			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tibia fracture			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 224 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis uraemic			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lupus			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Epilepsy			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized tonic-clonic seizure			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 224 (0.45%)	6 / 224 (2.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 224 (1.34%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 224 (0.89%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow toxicity			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglobulinaemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 224 (0.89%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 224 (1.34%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 224 (0.89%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 224 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiploic appendagitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis gastrointestinal			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (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			
Angioedema			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema annulare			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus rash			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	2 / 224 (0.89%)	8 / 224 (3.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute kidney injury			
subjects affected / exposed	2 / 224 (0.89%)	5 / 224 (2.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)	
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 / 224 (0.89%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 224 (0.89%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders				
Systemic lupus erythematosus				
subjects affected / exposed	1 / 224 (0.45%)	4 / 224 (1.79%)		
occurrences causally related to treatment / all	0 / 1	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Arthralgia				
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Back pain				
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Flank pain				
subjects affected / exposed	0 / 224 (0.00%)	2 / 224 (0.89%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intervertebral disc protrusion				
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (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	0 / 224 (0.00%)	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Oligoarthritis				
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Osteonecrosis				
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rhabdomyolysis				

subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	10 / 224 (4.46%)	10 / 224 (4.46%)	
occurrences causally related to treatment / all	3 / 11	5 / 11	
deaths causally related to treatment / all	2 / 3	0 / 1	
Herpes zoster			
subjects affected / exposed	4 / 224 (1.79%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 224 (0.89%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	2 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 224 (1.79%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 224 (0.00%)	5 / 224 (2.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 224 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 224 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subcutaneous abscess			
subjects affected / exposed	2 / 224 (0.89%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	2 / 224 (0.89%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 224 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone abscess			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis viral			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
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	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			

subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes oesophagitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary nocardiosis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhodococcus infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal abscess			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster viral infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 224 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			

subjects affected / exposed	1 / 224 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 224 (0.45%)	
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	Belimumab 10 mg/kg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 224 (83.04%)	191 / 224 (85.27%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 224 (5.36%)	20 / 224 (8.93%)	
occurrences (all)	14	23	
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 224 (15.18%)	35 / 224 (15.63%)	
occurrences (all)	51	57	
Dizziness			
subjects affected / exposed	13 / 224 (5.80%)	19 / 224 (8.48%)	
occurrences (all)	18	21	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 224 (4.91%)	17 / 224 (7.59%)	
occurrences (all)	14	20	
Oedema peripheral			
subjects affected / exposed	16 / 224 (7.14%)	13 / 224 (5.80%)	
occurrences (all)	23	17	
Fatigue			
subjects affected / exposed	12 / 224 (5.36%)	14 / 224 (6.25%)	
occurrences (all)	12	15	
Oedema			

subjects affected / exposed	9 / 224 (4.02%)	12 / 224 (5.36%)	
occurrences (all)	9	15	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 224 (5.80%)	23 / 224 (10.27%)	
occurrences (all)	16	26	
Leukopenia			
subjects affected / exposed	15 / 224 (6.70%)	19 / 224 (8.48%)	
occurrences (all)	28	29	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	45 / 224 (20.09%)	48 / 224 (21.43%)	
occurrences (all)	59	56	
Nausea			
subjects affected / exposed	21 / 224 (9.38%)	24 / 224 (10.71%)	
occurrences (all)	28	33	
Vomiting			
subjects affected / exposed	16 / 224 (7.14%)	16 / 224 (7.14%)	
occurrences (all)	25	21	
Abdominal pain			
subjects affected / exposed	12 / 224 (5.36%)	13 / 224 (5.80%)	
occurrences (all)	15	13	
Dyspepsia			
subjects affected / exposed	9 / 224 (4.02%)	15 / 224 (6.70%)	
occurrences (all)	10	18	
Abdominal pain upper			
subjects affected / exposed	16 / 224 (7.14%)	6 / 224 (2.68%)	
occurrences (all)	16	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 224 (13.39%)	21 / 224 (9.38%)	
occurrences (all)	38	23	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	12 / 224 (5.36%)	9 / 224 (4.02%)	
occurrences (all)	13	11	

Rash			
subjects affected / exposed	23 / 224 (10.27%)	17 / 224 (7.59%)	
occurrences (all)	31	18	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 224 (4.46%)	18 / 224 (8.04%)	
occurrences (all)	10	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 224 (11.61%)	32 / 224 (14.29%)	
occurrences (all)	44	52	
Back pain			
subjects affected / exposed	17 / 224 (7.59%)	17 / 224 (7.59%)	
occurrences (all)	24	17	
Muscle spasms			
subjects affected / exposed	18 / 224 (8.04%)	15 / 224 (6.70%)	
occurrences (all)	25	18	
Pain in extremity			
subjects affected / exposed	12 / 224 (5.36%)	8 / 224 (3.57%)	
occurrences (all)	14	9	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	81 / 224 (36.16%)	74 / 224 (33.04%)	
occurrences (all)	159	134	
Urinary tract infection			
subjects affected / exposed	43 / 224 (19.20%)	37 / 224 (16.52%)	
occurrences (all)	73	72	
Nasopharyngitis			
subjects affected / exposed	35 / 224 (15.63%)	31 / 224 (13.84%)	
occurrences (all)	60	50	
Gastroenteritis			
subjects affected / exposed	21 / 224 (9.38%)	23 / 224 (10.27%)	
occurrences (all)	24	28	
Bronchitis			
subjects affected / exposed	18 / 224 (8.04%)	19 / 224 (8.48%)	
occurrences (all)	24	26	

Herpes zoster			
subjects affected / exposed	17 / 224 (7.59%)	19 / 224 (8.48%)	
occurrences (all)	17	20	
Conjunctivitis			
subjects affected / exposed	13 / 224 (5.80%)	5 / 224 (2.23%)	
occurrences (all)	13	5	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	24 / 224 (10.71%)	20 / 224 (8.93%)	
occurrences (all)	36	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2012	Amendment 01: Applied to all countries and sites. The protocol was modified to clarify exclusion criteria, concurrent medications and standard of care, addition of anti-malarials, and use of corticosteroids. There were also changes to prohibited medications and non-drug therapies, live vaccines, screening procedures, and the double-blind treatment period and study calendar. An open-label extension replaced the continuation phase. An exploratory analysis of urinary biomarkers related to lupus nephritis was added. Clarifications were made to the withdrawal of study treatment and adverse event reporting sections. The endpoints and statistical analysis sections were updated to reflect changes made in other sections of the protocol.
08 March 2012	Amendment 02: Applied to all countries and sites. The protocol was modified to require participants to remain under clinical supervision for 3 hours after completion of the first 2 infusions. Results for biological markers measured by florescence activated cell sorting (FACS) were added to the list of laboratory results not provided to study sites. Language describing participant un-blinding in the protocol was amended. Language regarding the body weight used for dose calculation was corrected.
11 February 2014	Amendment 03: Applied to all countries and sites. In this amendment the protocol was modified to expand Hepatitis B serology testing, to exclude participants who tested positive according to the criteria specified, and to specify hepatitis C screening. Screening and induction initiation windows were extended and details were added for eligibility criteria pertaining to various laboratory parameters. Clarification was added for screening for active or latent infections. A belimumab Benefit and Risk Assessment, and a preliminary assessment specific to the lupus nephritis participant population were added. Information on non-acute delayed type hypersensitivity reaction and symptoms was added. Instructions for monitoring and managing cases of Grade 4 immunoglobulin G (IgG) were clarified. The concurrent medication section was modified. Steroid rescue for non-renal systemic lupus erythematosus (SLE) disease activity and non-SLE disease activity was revised. Timing of pharmacokinetic sampling in participants who withdrew from the study was clarified. A new section was added to clarify management of participants with liver chemistry events during the study. Reason for treatment withdrawal was modified. Participant un-blinding information was updated. The adverse events section was modified for consistency. Progressive multifocal leukoencephalopathy (PML) text was updated. The Independent Data Monitoring Committee (IDMC) was also to monitor all serious adverse events (SAEs). New appendices were added to provide the questionnaires for the possible suicidality-related history questionnaire (PSRHQ), the possible suicidality-related questionnaire (PSRQ), and the Country-specific Requirements for Thailand.
16 March 2015	Amendment 05: Applied in all countries and sites, except for those with a local version amendment. Eligibility criteria, exclusion criteria, and relevant sections were modified to allow patients who initiated an induction recently to be considered for enrollment. The Risk-Benefit and concomitant medications sections were updated. A urine pregnancy test was added at the 8-week follow-up visit, and any pregnancy that occurred through 16 weeks following the last dose of IP was to be reported. The section on liver safety evaluation was replaced for consistency with GlaxoSmithKline (GSK) standards. Additional Hepatitis B monitoring was added.

25 April 2017	Amendment 06: Applied in all countries and sites, except for those with a local version amendment. The renal response definition used for key efficacy endpoints evaluation was modified. Calculated glomerular filtration rate (GFR) was changed to estimated GFR to be used for all renal function evaluations. Time to first renal flare was added as a major secondary efficacy endpoint. Clarification was added regarding timing of the renal biopsy. Clarifications regarding the target sample size and sample size calculations were added. Contraception requirements were updated. The Benefit-Risk section text was updated in line with current belimumab safety information. The concomitant medications section was updated to clarify concurrent medication rules applicable to the double-blind period. At the request of the IDMC the requirement to review Grade 4 IgG reductions on an expedited basis was removed. The Van Elteren test was replaced with a Rank analysis of covariance (ANCOVA) for the primary and major secondary endpoints analysis. Updates were also made to how missing values will be handled, how the sensitivity analyses will be performed, and additional other efficacy endpoints were defined. The rate of renal flare from Week 24, time to first renal flare from Week 52, and the rate of renal flare from Week 52 were also added as other efficacy endpoints and for some of the other efficacy endpoints, clarification text has been added.
24 January 2019	Amendment 07: Applied in all countries and sites, except for those with a local version amendment. In this amendment the primary endpoint and the time to renal flare at Week 24 endpoint were changed. The testing hierarchy and the analysis methodology of the major secondary endpoints was revised accordingly. Power calculations were added to the sample size section. A subgroup for Baseline renal biopsy class was added. Other efficacy endpoints were updated to be consistent with and supportive of the revised testing hierarchy. Endpoints inadvertently omitted were added to other efficacy endpoints. The timeframe for pregnancy reporting was updated to sponsor requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported