Clinical trial results:
A Multi-center, Randomized Parallel Group, Placebo-Controlled Double-Blind Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE)

Summary

EudraCT number	2011-000368-88
Trial protocol	GB ES PL NL IT Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	08 August 2018
First version publication date	08 August 2018

Trial information

Trial identification

Sponsor protocol code	114055

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,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000520-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	16 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety, tolerability, pharmacokinetics, efficacy of belimumab and to evaluate the effects of belimumab on the quality of life in the pediatric SLE population.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Peru: 14
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	93
EEA total number of subjects	21

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	0

months)	
Children (2-11 years)	13
Adolescents (12-17 years)	80
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 93 pediatric participants with Systemic Lupus Erythematosus (SLE) were enrolled at 29 study centers in 10 different countries. This was a multi-center study to evaluate the safety, efficacy and pharmacokinetics of belimumab plus background standard therapy. The results presented are based on Part A (double blind).

Pre-assignment

Screening details:

The study consisted of three separate phases: Randomized, placebo-controlled, double-blind 52-week treatment phase (Part A), Long term belimumab open label safety follow up for participants who completed Part A (Part B) and Long term safety follow-up phase for participants who were withdrawn from Part A or Part B at any time (Part C).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received saline infusion (placebo) intravenously monthly for 48 weeks on a background of standard of care

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

Dosage and administration details:

Normal Saline intravenously.

Arm title	Belimumab 10 mg/kg

Arm description:

Participants received 10 milligrams per kilograms (mg/kg) reconstituted solution intravenously monthly for 48 weeks on a background of standard of care.

Arm type	Experimental
Investigational medicinal product name	Benlysta (belimumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Belimumab (10 mg/kg or adjusted dose) intravenously.

Number of subjects in period 1	Placebo	Belimumab 10 mg/kg
Started	40	53
Completed	31	45
Not completed	9	8
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	1
Physician decision	-	3
Adverse event, non-fatal	4	3
Lack of efficacy	1	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received saline infusion (placebo) intravenously monthly for 48 weeks on a background of standard of care	
Reporting group title	Belimumab 10 mg/kg
Reporting group description:	
Participants received 10 milligrams per kilograms (mg/kg) reconstituted solution intravenously monthly for 48 weeks on a background of standard of care.	

Reporting group values	Placebo	Belimumab 10 mg/kg	Total
Number of subjects	40	53	93
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	14.8	13.5	
standard deviation	± 2.17	± 2.59	-
Gender categorical			
Units: Subjects			
Female	39	49	88
Male	1	4	5
Race/Ethnicity, Customized			
Units: Subjects			
Race White - White/Caucasian/European Heritage	21	27	48
Race Asian	6	8	14
Race African American/African Heritage	2	3	5
Race American Indian or Alaskan Native	11	15	26

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received saline infusion (placebo) intravenously monthly for 48 weeks on a background of standard of care	
Reporting group title	Belimumab 10 mg/kg
Reporting group description:	
Participants received 10 milligrams per kilograms (mg/kg) reconstituted solution intravenously monthly for 48 weeks on a background of standard of care.	

Primary: Percentage of participants with SLE Responder Index (SRI) response at Week 52

End point title	Percentage of participants with SLE Responder Index (SRI) response at Week 52
End point description:	
SRI response is defined as >=4 point reduction, from Baseline in safety of estrogen in lupus national assessment (SELENA) systemic lupus erythematosus disease activity index (SLEDAI) score, no worsening (increase of <0.30 points from Baseline) in physician's global assessment (PGA) and no new British Isles Lupus Assessment Group of SLE clinics (BILAG) A organ domain score or 2 new BILAG B organ domain scores compared with Baseline. Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, Baseline SELENA SLEDAI score (<=12 vs. >=13). Percentage of participants with SRI response at Week 52 of Part A were reported. Intent-to-Treat Population comprised of all participants who were randomized and treated with at least one dose of study agent in Part A. One participant had missing data at Baseline and therefore, could not be included in the analysis.	
End point type	Primary
End point timeframe:	
Week 52	

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[1]	53[2]		
Units: Percentage of participants				
number (not applicable)				
Percentage of participants	43.6	52.8		

Notes:

[1] - Intent-to-Treat Population

[2] - Intent-to-Treat Population

Statistical analyses

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

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	3.46

Secondary: Percentage of participants meeting Pediatric Rheumatology International Trials Organization (PRINTO)/ American College of Rheumatology (ACR) Juvenile SLE Response Evaluation criteria for improvement in juvenile SLE at Week 52 using definition 1 and 2

End point title	Percentage of participants meeting Pediatric Rheumatology International Trials Organization (PRINTO)/ American College of Rheumatology (ACR) Juvenile SLE Response Evaluation criteria for improvement in juvenile SLE at Week 52 using definition 1 and 2

End point description:

Percentage of participants meeting PRINTO/ACR Juvenile SLE Response Evaluation criteria for improvement in juvenile SLE using two different PRINTO/ACR Juvenile SLE Response Evaluation definitions of improvement that is Definition 1: At least 50% improvement in any 2 of 5 endpoints below and no more than 1 of the remaining worsening by more than 30% and Definition 2: At least 30% improvement in 3 of 5 endpoints below and no more than 1 of the remaining worsening more than 30%. Endpoints were: 1. Percent change in Parent's Global Assessment (ParentGA) at Week 52, 2. Percent change in PGA at Week 52, 3. Percent change in SELENA SLEDAI score at Week 52, 4. Percent change in Pediatric Quality of Life Inventory (PedsQL) physical functioning domain at Week 52, 5. Percent change in 24 hour proteinuria at Week 52 (gram/24hour equivalent by spot urine protein to creatinine ratio).

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	40[3]	53[4]		
Units: Percentage of participants				
number (not applicable)				
Definition 1	35.0	60.4		
Definition 2	27.5	52.8		

Notes:

[3] - Intent-to-Treat Population

[4] - Intent-to-Treat Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Definition 1

Comparison groups	Placebo v Belimumab 10 mg/kg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	6.54

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Definition 2	
Comparison groups	Placebo v Belimumab 10 mg/kg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	7.17

Secondary: Percent change from Baseline in ParentGA at Week 52

End point title	Percent change from Baseline in ParentGA at Week 52

End point description:

ParentGA assesses the participant’s overall well-being at the moment rated on a 21-numbered circle visual analog scale (VAS; 0 - very well, 10 - very poorly). Baseline was defined as measurements at Day 0. Percent change from Baseline was calculated by subtracting the Baseline value from value at Week 52 divided by the Baseline value X 100. Last Observation Carried Forward (LOCF) was used. Eight participants had a score of zero at Baseline and therefore, could not be included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[5]	47[6]		
Units: Percent change				
median (full range (min-max))				
Percent change	-23.61 (-95.0 to 600.0)	-53.85 (-100.0 to 900.0)		

Notes:

[5] - Intent-to-Treat Population

[6] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in PGA at Week 52

End point title	Percent change from Baseline in PGA at Week 52

End point description:

The PGA is a 10 centimeter (cm) visual analogue scale (VAS), anchored at 0 (none) and 3 (severe), designed for the physician to indicate the participant's overall disease activity at a particular visit as part of the validated SELENA SLEDAI index. Primary investigator or a subinvestigator scored the PGA for the participant, and same person evaluated the participant each time. Baseline was defined as measurements at Day 0. Percent change from Baseline was calculated by subtracting the Baseline value from value at Week 52 divided by the Baseline value X 100. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[7]	53[8]		
Units: Percent change				
arithmetic mean (standard deviation)				
Percent change	-48.802 (± 42.0423)	-56.525 (± 43.7939)		

Notes:

[7] - Intent-to-Treat Population

[8] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in SELENA SLEDAI at Week 52

End point title	Percent change from Baseline in SELENA SLEDAI at Week 52

End point description:

The SELENA SLEDAI score is a weighted index for assessing SLE disease activity in which signs and symptoms, laboratory tests and physician's assessment for each of 9 organ system were given a weighted score and summed if present at the time of the visit or in the preceding 10 days. A SELENA SLEDAI score of 0 would suggest no lupus activity; while a score of 105 is the maximum calculable if all items were scored as being present from active lupus. A decrease of 4 points or more equates to a

clinically meaningful improvement. Baseline was defined as measurements at Day 0. Percent change from Baseline was calculated by subtracting the Baseline value from value at Week 52 divided by the Baseline value X 100. One participant had missing data at Baseline and therefore, could not be included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[9]	53[10]		
Units: Percent change				
arithmetic mean (standard deviation)				
Percent change	-38.0 (± 39.50)	-43.3 (± 43.73)		

Notes:

[9] - Intent-to-Treat Population

[10] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in PedsQL Physical Functioning Domain Score at Week 52

End point title	Percent change from Baseline in PedsQL Physical Functioning Domain Score at Week 52

End point description:

The PedsQL is a generic quality of life scale validated for the pediatric population which consists of 23 items, encompassing 4 health domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). From the raw scores of the 23 items, a total summary score and individual domain scores can be calculated. The total and domain scores are each transformed on a 0 to 100 score with higher scores indicating higher quality of life. For Physical Functioning Domain scale, score was from 0 to 100 where, 0 indicates lower quality of life and 100 indicates greater quality of life. Baseline was defined as measurements at Day 0. Percent change from Baseline was calculated by subtracting the Baseline value from value at Week 52 divided by the Baseline Value X 100. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[11]	53[12]		
Units: Percent change				
median (full range (min-max))				
Percent change	12.5 (-53 to 575)	10.5 (-100 to 280)		

Notes:

[11] - Intent-to-Treat Population

[12] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in proteinuria at Week 52

End point title	Percent change from Baseline in proteinuria at Week 52

End point description:

Percent change from Baseline in proteinuria was calculated. The percent change from baseline to Week 52 in 24 hour proteinuria was analyzed using summary statistics and 95% confidence intervals, without any adjustment for covariates. Baseline was defined as measurements at Day 0. Percent change from Baseline was calculated by subtracting the Baseline value from value at Week 52 divided by the Baseline Value X 100. LOCF was used.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[13]	53[14]		
Units: Percent Change				
median (full range (min-max))				
Percent Change	7.0920 (-90.568 to 570.149)	-2.1277 (-85.073 to 1681.884)		

Notes:

[13] - Intent-to-Treat Population

[14] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a sustained SRI response

End point title	Percentage of participants with a sustained SRI response

End point description:

Sustained SRI response was defined as having a response on the primary efficacy endpoint at Weeks 44, 48, and 52. Data for percentage of participants with a sustained SRI response was presented. Drop Outs and Treatment Failures were considered Non-Responders. Only those participants with data available at specific time point were analyzed.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[15]	53[16]		
Units: Percentage of participants				
number (not applicable)				
Percentage of participants	41.0	43.4		

Notes:

[15] - Intent-to-Treat Population

[16] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a sustained ParentGA response

End point title	Percentage of participants with a sustained ParentGA response

End point description:

Sustained ParentGA response was defined as having >0.7 improvement at Weeks 44, 48, and 52 compared at Baseline. Data for percentage of participants with a sustained ParentGA response was presented. Thirteen participants had a score of <=0.7 at Baseline and therefore, could not be included in the analysis.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[17]	44[18]		
Units: Percentage of Participants				
number (not applicable)				
Percentage of Participants	33.3	59.1		

Notes:

[17] - Intent-to-Treat Population

[18] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any

untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, 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 AEs and SAEs have been reported.

End point type	Secondary

End point timeframe:

Up to 60 weeks

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[19]	53[20]		
Units: Participants				
AEs	33	42		
SAEs	14	9		

Notes:

[19] - Intent-to-Treat Population

[20] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration at steady state (Cmax, ss) and minimum concentration at steady state (Cmin, ss)

End point title	Maximum concentration at steady state (Cmax, ss) and minimum concentration at steady state (Cmin, ss)[21]

End point description:

The pharmacokinetic (PK) population comprised all participants included in the As- Treated population for whom at least one post belimumab treatment PK sample was obtained and analyzed. The PK model was fitted to the observed serum concentration-time data. The maximum (Cmax) and minimum (Cmin) concentrations reported in this table are model derived values at ss, assuming a 10 mg/kg dose administered once every 28 days.

End point type	Secondary

End point timeframe:

28-days dosing interval at steady state

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Belimumab 10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	53[22]			
Units: Micrograms per milliliter				
geometric mean (geometric coefficient of variation)				
Cmax, ss	315 (± 31.2)			
Cmin, ss	50 (± 68.3)			

Notes:

[22] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Area under curve of Belimumab at steady state (AUC, ss)

End point title	Area under curve of Belimumab at steady state (AUC, ss)[23]

End point description:

The PK model was fitted to the observed serum concentration-time data. The AUC values reported in this table are model derived values at ss, assuming a 10 mg/kg dose administered once every 28 days.

End point type	Secondary

End point timeframe:

28-days dosing interval at steady state

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Belimumab 10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	53[24]			
Units: Micrograms per milliliter				
geometric mean (geometric coefficient of variation)				
Micrograms per milliliter	3012 (± 43.2)			

Notes:

[24] - PK Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from start of the study to the follow up visit (Up to 60 weeks).

Adverse event reporting additional description:

Intent-to-Treat Population was used to collect adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Belimumab 10 mg/kg

Reporting group description:

Participants received 10 milligrams per kilograms (mg/kg) reconstituted solution intravenously monthly for 48 weeks on a background of standard of care.

Reporting group title	Placebo

Reporting group description:

Participants received saline infusion (placebo) intravenously monthly for 48 weeks on a background of standard of care

Serious adverse events	Belimumab 10 mg/kg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 53 (16.98%)	14 / 40 (35.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic intracranial hypertension			

subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vasculitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vasculitis gastrointestinal			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (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			
Rash			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	2 / 53 (3.77%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLE arthritis			

subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (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			
Herpes zoster			
subjects affected / exposed	1 / 53 (1.89%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 53 (1.89%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 53 (0.00%)	1 / 40 (2.50%)	
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	36 / 53 (67.92%)	27 / 40 (67.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 53 (7.55%)	4 / 40 (10.00%)	
occurrences (all)	4	5	
Pyrexia			
subjects affected / exposed	2 / 53 (3.77%)	3 / 40 (7.50%)	
occurrences (all)	2	10	
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	2 / 40 (5.00%)	
occurrences (all)	2	4	
Reproductive system and breast disorders			

Menorrhagia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Dysmenorrhoea			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	4 / 53 (7.55%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Cough			
subjects affected / exposed	3 / 53 (5.66%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Oropharyngeal pain			
subjects affected / exposed	3 / 53 (5.66%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Dyspnoea			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Suicidal ideation			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Investigations			
Transaminases increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Blood immunoglobulin G decreased			
subjects affected / exposed	1 / 53 (1.89%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			

subjects affected / exposed	7 / 53 (13.21%)	10 / 40 (25.00%)	
occurrences (all)	9	17	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 53 (3.77%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Neutropenia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Anaemia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 53 (13.21%)	3 / 40 (7.50%)	
occurrences (all)	9	5	
Nausea			
subjects affected / exposed	5 / 53 (9.43%)	3 / 40 (7.50%)	
occurrences (all)	6	4	
Abdominal pain			
subjects affected / exposed	3 / 53 (5.66%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Vomiting			
subjects affected / exposed	2 / 53 (3.77%)	3 / 40 (7.50%)	
occurrences (all)	2	4	
Dyspepsia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 40 (7.50%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 53 (5.66%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	1 / 53 (1.89%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	3 / 53 (5.66%)	4 / 40 (10.00%)	
occurrences (all)	4	10	
Back pain			
subjects affected / exposed	2 / 53 (3.77%)	3 / 40 (7.50%)	
occurrences (all)	3	4	
Pain in extremity			
subjects affected / exposed	2 / 53 (3.77%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Joint swelling			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 53 (16.98%)	8 / 40 (20.00%)	
occurrences (all)	14	11	
Upper respiratory tract infection			
subjects affected / exposed	6 / 53 (11.32%)	8 / 40 (20.00%)	
occurrences (all)	8	8	
Herpes zoster			
subjects affected / exposed	4 / 53 (7.55%)	2 / 40 (5.00%)	
occurrences (all)	6	2	
Pharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Gastroenteritis			
subjects affected / exposed	2 / 53 (3.77%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	4 / 40 (10.00%)	
occurrences (all)	2	8	
Bronchitis			
subjects affected / exposed	1 / 53 (1.89%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Conjunctivitis			

subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	4	
Influenza			
subjects affected / exposed	0 / 53 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2012	Amendment No. 1: Updated Medical Monitor information. Additional pharmacokinetic samples were taken for children not in Cohort 1 or 2. Addition of three hours observation post infusion was done. Time and Events Table including immunogenicity, vaccine titer procedure and physical assessments was updated. Other Secondary Endpoints were updated. Study Conclusion criteria was added. Minor typographical errors corrected.
31 January 2013	Amendment No. 2: Included the following changes: Exclusion Criterion #1 excludes if B cell targeted therapy is within 1 year of Day 0 and Exclusion #23 omitting HCV confirmation RIBA assay. Extra visits for collection of large blood sample collection were Allowed. Addition of 3 hours observation post infusion for first 3 infusions in Part B. The investigational product may be delivered in either 100 mL or 250mL of saline. Minor typographical errors corrected.
18 February 2014	Amendment No. 3: Included the following changes: Updated safety information on PML and Delayed Hypersensitivity Reaction. Changed the exclusion for high dose steroid use from 90 days to 60 days prior to Baseline. Clarification of treatment failure and study withdrawal criteria and Clarification of procedure for destruction of investigational product and used vials was updated. Added a home pregnancy test and follow up phone call at 16 Week post last dose. Extended visit window in Part B and Part C. Minor typographical and formatting errors corrected.
03 November 2014	Amendment No. 4: Changed the Screening inclusion criterion SELENA SLEDAI to >= 6. Changed randomization strata for Cohort 3 to stratification by age and SELENA SLEDAI 6-12 and >=13. Added requirement that 50% of participants were recruited with SS score of >= 8. Changed exclusion #4 intravenous (IV) cyclophosphamide within 60 days of Day 0. Added allowance for stable Grade 3 lymphopenia with exclusion #24. Updated GSK liver chemistry stopping criteria and added of study drug restart criteria. Clarification of laboratory tests needed to complete SS and BILAG assessments. Added immunogenicity testing in Part C. Clarification of NSAIDs use in Part A. Minor typographical errors corrected.
22 April 2015	Amendment No. 5: Country Specific Amendment for Russian Federation: Restart of study treatment after liver event is not applicable to Investigator sites in Russia. Updated phone number of back-up Medical Monitor.
12 December 2016	Amendment No. 6: Updated Author information, Medical Monitor information and site address. Total study target amended to 'at least 70' from 100 participants. Estimates for sample size re-estimation add to the protocol. Target for participants less than 13 years old amended to at least 14 from 20. Target for Cohort 2 amended from 12 to "at least 10". PedsQL amended in time and events table such that it is instructed to be taken at Day 0. Anti-dsDNA; C3/C4 added to time and events table for 6 month visits in Part B. Deleted immunogenicity sample collection once a subject has left the study. Collect additional PK samples in the participants in Japan at the first 12 week and 6 month visit in Part B. Minor typographical errors corrected. Clarification of reporting of AEs, SAEs, and AESI. Change in Part C from "non-belimumab phase" to "safety follow up phase".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported