Clinical trial results:
Safety and efficacy of Belimumab After B cell depletion therapy in systemic LUPUS erythematosus (BEAT LUPUS)

Summary

EudraCT number	2015-005543-14
Trial protocol	GB
Global end of trial date	03 December 2020

Results information

Result version number	v1 (current)
This version publication date	17 December 2021
First version publication date	17 December 2021

Trial information

Trial identification

Sponsor protocol code	CTU/2013/096

Additional study identifiers

ISRCTN number	ISRCTN47873003
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS ID: 195085

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Enquiries, The Comprehensive Clinical Trials Unit, University College London, 44 020 7907 4669, cctu-enquiries@ucl.ac.uk
Scientific contact	Enquiries, The Comprehensive Clinical Trials Unit, University College London, 44 020 7907 4669, cctu-enquiries@ucl.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2020
Global end of trial reached?	Yes
Global end of trial date	03 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety, efficacy, and immunological effects of anti-BAFF treatment Belimumab in lupus patients after B cell depletion therapy. To obtain preliminary evidence for efficacy of the anti-BAFF therapeutic belimumab after rituximab in SLE.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Although Rituximab therapy is given as standard of care, the sequential combination of Belimumab soon after Rituximab, has never been given before and so this was a phase II trial assessing the safety and efficacy of this strategy. Adverse Events were collected throughout the trial and treated accordingly. Participants were reviewed every 4 weeks when treatment was administered, up until 52 weeks of treatment. The protocol included steps to take in cases of abnormal liver chemistry results. To manage hypersensitivity reactions (infusion reactions/anaphylaxis) participants were monitored for 3 hours after completing each of the first 2 infusions (when it was more frequently to occur). For subsequent infusions, participants were monitored during and for an appropriate period of time after completing the infusion as per local policies. In cases of severe reactions, study treatment was discontinued immediately and the appropriate medical therapy administered. Protocol pre-defined reasons for discontinuation of treatment were in place. As participation was voluntary, participants were free to discontinue at any given time without giving reason and without it affecting their normal standard of care.

Background therapy:

All participants were permitted to receive Rituximab treatment (B cell depletion therapy) as standard of care and had to have received two cycles after being screened and consented, with the first cycle occurring 4-8 weeks prior to randomisation.

Evidence for comparator: -

Actual start date of recruitment	08 November 2016
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	United Kingdom: 52
Worldwide total number of subjects	52
EEA total number of subjects	0

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)	51
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started 8th November 2016 and ended 29th March 2019. Participants were recruited from 16 specialist lupus centres in England. Participants were randomised 1:1 (Belimumab or Placebo). Participants had to be due their first cycle of Rituximab therapy (standard of care) 4-8 weeks prior to randomisation.

Pre-assignment

Screening details:

Systemic Lupus Erythematosus (SLE) patients with active lupus resistant to conventional therapy and receiving B cell depletion therapy (Rituximab) as standard of care. Participants with anti-dsDNA antibodies detectable in the past 5 years. Written informed consent obtained prior to any trial activities commencing. Standard of care bloods assessed.

Period 1

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

Blinding implementation details:

Participants were randomised 1:1 ratio to receive either Belimumab or Placebo treatment using a secure online randomisation service provider, Sealed Envelope (SE). Randomisation was performed using minimisation, incorporating a random element to maximise balance in the stratifying variables. The unblinded trial statistician produced a unique list of infusion codes and this was incorporated into SE and provided to the unblinded pharmacists at sites.

Arms

Are arms mutually exclusive?	Yes
Arm title	Belimumab

Arm description:

IV infusion administered according to the standard dosage regime. 10mg/kg at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).

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

Dosage and administration details:

400mg single use vial of Belimumab reconstituted and diluted prior to administration. 10mg/kg administered over a period of 1 hour at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).

Arm title	Placebo (Saline)

Arm description:

Sodium Chloride (0.9% solution) 10mg/kg IV infusions at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	Sodium Chloride 0.9% solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg/kg IV infusions at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).

Number of subjects in period 1	Belimumab	Placebo (Saline)
Started	26	26
Completed	16	16
Not completed	10	10
Consent withdrawn by subject	5	2
Adverse event, non-fatal	5	7
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Belimumab
Reporting group description:	
IV infusion administered according to the standard dosage regime. 10mg/kg at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).	
Reporting group title	Placebo (Saline)
Reporting group description:	
Sodium Chloride (0.9% solution) 10mg/kg IV infusions at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).	

Reporting group values	Belimumab	Placebo (Saline)	Total
Number of subjects	26	26	52
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	38	41	
standard deviation	± 11.4	± 10.6	-
Gender categorical Units: Subjects			
Female	21	23	44
Male	5	3	8
Ethnicity Units: Subjects			
White	13	17	30
Black	3	3	6
South Asian	4	2	6
Chinese	2	1	3
Other	4	3	7
Previous rituximab Units: Subjects			
Yes	6	8	14
No	20	18	38
Previous rituximab within 2 years from screening Units: Subjects			

Yes	4	3	7
No	22	23	45
Concomitant Mycophenolate at screening and randomization Units: Subjects			
Yes	19	15	34
No	7	11	18
Concomitant Azathioprine at screening and randomization Units: Subjects			
Yes	2	2	4
No	24	24	48
Concomitant Methotrexate at screening and randomization Units: Subjects			
Yes	3	2	5
No	23	24	47
Concomitant Prednisolone at screening and randomization Units: Subjects			
Yes	22	24	46
No	4	2	6
Any concomitant immunosuppressant at screening and randomization Units: Subjects			
Yes	24	19	43
No	2	7	9
Receiving concomitant immunosuppressant or prednisolone at screening or randomization Units: Subjects			
Yes	24	26	50
No	2	0	2
Concomitant hydroxychloroquine at screening and randomization Units: Subjects			
Yes	17	20	37
No	9	6	15
Patients taking ≥7.5 mg of prednisolone per day at screening Units: Subjects			
Yes	14	18	32
No	12	8	20
Patients taking ≥7.5 mg of prednisolone per day at randomization Units: Subjects			
Yes	15	18	33
No	11	8	19
Patients taking ≥10 mg of prednisolone per day at screening and randomization Units: Subjects			
Yes	13	16	29
No	13	10	23
Organ involvement (BILAG-2004 A or B score) at screening or randomization -			

Constitutional Units: Subjects			
Yes	3	2	5
No	23	24	47
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Cardiorespiratory Units: Subjects			
Yes	4	6	10
No	22	20	42
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Mucocutaneous Units: Subjects			
Yes	13	14	27
No	13	12	25
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Musculoskeletal Units: Subjects			
Yes	11	9	20
No	15	17	32
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Neuropsychiatric Units: Subjects			
Yes	0	1	1
No	26	25	51
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Ophthalmic Units: Subjects			
Yes	1	0	1
No	25	26	51
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Gastrointestinal Units: Subjects			
Yes	0	0	0
No	26	26	52
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Renal Units: Subjects			
Yes	10	10	20
No	16	16	32
Organ involvement (BILAG-2004 A or B score) at screening or randomization - Hematologic Units: Subjects			
Yes	1	0	1
No	25	26	51
BILAG-2004 score at randomization - ≥1 A score Units: Subjects			
Yes	6	8	14

No	20	18	38
BILAG-2004 score at randomization - ≥1 A score or 2 B scores Units: Subjects			
Yes	13	9	22
No	13	17	30
BILAG-2004 score at randomization - ≥1 A score, 2 B scores, or 1 B score Units: Subjects			
Yes	23	20	43
No	3	6	9
Positive anti-dsDNA IgG antibody result at screening Units: Subjects			
Yes	24	23	47
No	2	3	5
Low complement C3 level at screening Units: Subjects			
Yes	11	13	24
No	15	13	28
Patients with CD19 count <0.01 x 10^9/L at randomization Units: Subjects			
Yes	22	22	44
No	4	4	8
Disease duration at screening Units: Years			
arithmetic mean	11.8	9.2	
standard deviation	± 8.8	± 7.4	-
Time between screening and randomization Units: Days			
arithmetic mean	44.7	41.8	
standard deviation	± 9.4	± 9.3	-
Daily prednisolone dose at screening Units: mg/day			
arithmetic mean	13.3	14.9	
standard deviation	± 9.0	± 9.8	-
Daily prednisolone dose at randomization Units: mg/day			
arithmetic mean	12.9	12.5	
standard deviation	± 7.7	± 6.7	-
IgG anti-dsDNA level at screening Units: IU/mL			
arithmetic mean	282	229	
standard deviation	± 281	± 238	-

End points

End points reporting groups

Reporting group title	Belimumab
Reporting group description:	
IV infusion administered according to the standard dosage regime. 10mg/kg at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).	
Reporting group title	Placebo (Saline)
Reporting group description:	
Sodium Chloride (0.9% solution) 10mg/kg IV infusions at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).	

Primary: IgG anti-dsDNA antibody levels

End point title	IgG anti-dsDNA antibody levels
End point description:	
Serum total IgG anti-dsDNA antibody levels (normal value <20 IU/mL) were analyzed by a commercially available enzyme-linked immunosorbent assay (Abnova) in a central laboratory at University College London.	
End point type	Primary
End point timeframe:	
Randomization to week 52	

End point values	Belimumab	Placebo (Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: UI/mL				
geometric mean (confidence interval 95%)	47 (25 to 88)	103 (49 to 213)		

Attachments (see zip file)	Serum IgG anti-dsDNA antibody

Statistical analyses

Statistical analysis title	ANCOVA at 52 weeks
Statistical analysis description:	
Linear regression analysis of covariance (ANCOVA) models were used to evaluate the difference in IgG anti-dsDNA antibody levels (log-transformed) between treatment groups at week 52. This model adjusted for CD19 count at randomization (<0.01 or ≥0.01 x 10^9/L), renal involvement at screening, and log anti-dsDNA levels at screening and randomization. The intention-to-treat analysis included all participants who were randomly assigned and contributed the relevant data at the timepoint analyzed.	
Comparison groups	Belimumab v Placebo (Saline)

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Percentage change
Point estimate	70
Confidence interval	
level	95 %
sides	2-sided
lower limit	46
upper limit	84

Secondary: Time to first severe flare

End point title	Time to first severe flare
End point description: Defined as ≥1 BILAG-2004 A score	
End point type	Secondary
End point timeframe: Over the 52 weeks of the trial	

End point values	Belimumab	Placebo (Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Severe flares				
number (not applicable)	26	26		

Statistical analyses

Statistical analysis title	Survival analysis
Comparison groups	Belimumab v Placebo (Saline)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.98

Secondary: Time to first severe flare or moderate flare	
End point title	Time to first severe flare or moderate flare
End point description: Defined as ≥1 BILAG-2004 A score or ≥2 BILAG-2004 B scores	
End point type	Secondary
End point timeframe: Over the 52 weeks of the trial	

End point values	Belimumab	Placebo (Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Severe/moderate flares				
number (not applicable)	26	26		

Statistical analyses

Statistical analysis title	Survival analysis
Comparison groups	Belimumab v Placebo (Saline)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All safety events (adverse event, adverse reaction, serious adverse event, serious adverse reaction) were to be reported from the time of randomisation until 30 days after the last treatment administration (end of study visit).

Adverse event reporting additional description:

Adverse events did not include:
- Medical or surgical procedures
- Pre-existing disease or condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Any new symptoms recorded on the BILAG 2004 Index which is related to SLE

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Belimumab

Reporting group description:

IV infusion administered according to the standard dosage regime. 10mg/kg at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).

Reporting group title	Placebo (Saline)

Reporting group description:

Sodium Chloride (0.9% solution) infusions at 2-week intervals for the first 3 infusions (Day 0, week 2 and week 4), and 4-weekly intervals thereafter for a total of 52 weeks (weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52).

Serious adverse events	Belimumab	Placebo (Saline)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 26 (23.08%)	6 / 26 (23.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Pulmonary embolism and deep venous thrombosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart failure			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocarditis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Tonic-clonic seizure			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial numbness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (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			
Lupus flare			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (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			
Acute kidney injury			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis/arthralgia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Lower respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft-tissue infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (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			
Hypoglycemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
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	Placebo (Saline)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 26 (92.31%)	24 / 26 (92.31%)	
Gastrointestinal disorders			
Diarrhea and constipation			
subjects affected / exposed	7 / 26 (26.92%)	4 / 26 (15.38%)	
occurrences (all)	20	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 26 (30.77%)	6 / 26 (23.08%)	
occurrences (all)	15	8	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Depression-like illness			
subjects affected / exposed	4 / 26 (15.38%)	5 / 26 (19.23%)	
occurrences (all)	4	5	
Musculoskeletal and connective tissue disorders			
Arthritis/arthralgia			
subjects affected / exposed	11 / 26 (42.31%)	12 / 26 (46.15%)	
occurrences (all)	27	29	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 26 (61.54%)	15 / 26 (57.69%)	
occurrences (all)	32	30	
Lower respiratory tract infection			
subjects affected / exposed	5 / 26 (19.23%)	9 / 26 (34.62%)	
occurrences (all)	6	12	
Urinary tract infection			
subjects affected / exposed	7 / 26 (26.92%)	5 / 26 (19.23%)	
occurrences (all)	12	9	
Herpes zoster/shingles			
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)	
occurrences (all)	3	6	
Other			

subjects affected / exposed occurrences (all)	13 / 26 (50.00%) 17	10 / 26 (38.46%) 20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2016	Protocol updated to v2.0 - first protocol version approved for global use.
25 April 2017	Protocol updated to v3.0 - Reduction to the frequency of some routine blood collection. Changes to secondary outcome with additional exploratory outcomes added. Extended time from 1st SOC infusion to 1st day of trial treatment. Additional exclusion criteria. Updated liver stopping criteria (as per funders requests). Treatment windows added.
15 May 2018	Protocol updated to v4.0 - Changes to inclusion #3 and clarification to inclusion #4. Additional text to address contraception use for male participants. Inclusion of Pregnancy monitoring PIS/ICF for participants and their partners. Length of trial shortened; follow up visits 60 and 64 removed.
13 March 2019	Protocol updated to v5.0 - Changes to Secondary Outcomes: - Specific times of follow-up at which secondary outcomes will be analysed have been added where these were previously missing. - Additional outcome; 'Proportion of participants' with any serious adverse events by week 52 has been added (secondary outcome #3). - Distinction made between 'severe' (2 BILAG B or 1 A) and 'moderate' flare (1 BILAG B with increase in any concomitant medication). - Additional outcome; the proportion of patients who have any 'severe or moderate' flare by 52 weeks (secondary outcome #6). - Steroids and immunosuppressant's allowed post-randomisation, added to secondary outcome #6 to capture all steroid changes and any potential moderate flares as per the trial Statistical Analysis Plan. - The analysis of EQ5D changed from analysis of the value at 52 weeks to analysis of the average value from randomisation as per the trial Statistical Analysis Plan. The statistical analysis plan has been amended to change the primary analysis to intention to treat, and added to two supportive analysis of the primary outcome; an analysis of whether trial treatment effects are mediated by changes in concomitant medication following randomisation, and an additional analysis of 52-week anti-dsDNA which excludes measurements taken after any increase in a concomitant medication due to flare (using instead the last anti-dsDNA measurement taken prior to this point). A secondary per-protocol analysis of the primary outcome will be also be done. Further clarification on the dose reduction of prednisolone following randomisation. Removal of anti-dsDNA collected and processed locally by sites at visit 17 (Participant Timeline section 6.6.). Further clarification added to Participant Timeline to address the trial assessments performed at withdrawal and patient reported severe flares. Updates to the roles/responsibilities of sponsor trial team and general admin changes throughout protocol.
02 September 2019	Protocol updated to v6.0 - To include information provided by GlaxoSmithKline (GSK) in regards to the risks of serious depression and/or suicidal Ideation or behaviour or self-Injury during treatment with belimumab. Update to contact details of the Sponsor's trial team at UCL CCTU.

25 February 2020	Protocol updated to v7.0 - The statistical analysis plan changed, following discussion about the analysis strategy and production of the BEAT-LUPUS statistical analysis plan (SAP) document in Autumn 2019. The following sections regarding the analysis have been changed in the protocol to match the new SAP: - The structured trial summary outcomes list has been updated - In Section 6.5 Outcomes, the outcomes list has been updated - Section 6.10 Data Collection, Management and Analysis has been changed to reflect changes to the SAP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34698499