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Belimumab after B Cell depletion therapy as a new treatment for patients with systemic lupus erythematosus (SLE)

Submission date
28/11/2016

Recruitment status
No longer recruiting

Registration date
28/11/2016

Overall study status
Completed

Last Edited
10/02/2023

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Systemic lupus erythematosus (SLE) is a long-term (chronic) disease which causes widespread inflammation (swelling) in the body. SLE occurs when the immune system attacks the body's own cells (autoimmune disease). A person's genes alongside other factors such as diet have been connected with the development and progression of the disease. B cell depletion therapy (normally rituximab) is used as part of standard of care in patients where their lupus is active. B cell depletion therapy removes a type of immune cell called B cells from the body. B cells can cause disease in lupus patients. Although patients respond to B cell depletion therapy the disease can quickly return. This is likely to be because a chemical (also known as a stimulating factor) called BAFF increases in the body once treatment ends, and switches the lupus back on. Belimumab is a drug that stops BAFF from working and has been shown to work in patients with lupus. The aim of this study is to investigate the safety and effectiveness of Belimumab in treating SLE.

Who can participate?
Men and women aged between 18-75 years old with systemic lupus erythematosus (SLE).

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive Belimumab through a drip at two week intervals for the first three doses and then at four week intervals until 52 weeks. Those in the second group receive normal saline (salt water) through a drip according to the same schedule. After 52 weeks, participants in both groups provide blood samples and complete questionnaires in order to find out how effective the belimumab treatment is compared to the placebo (dummy) treatment.

What are the possible benefits and risks of participating?
The benefits of participating include study patients having a regular review of their Lupus by an experienced Lupus specialist and information collected from this study will help improve the treatment of lupus. As Belimumab has not been given after drugs like rituximab in a research study it is not known if this is a safe combination. It is also possible that the risks of cancer,

infections and effects on mood (feeling anxious or depressed) could be increased when both Belimumab and rituximab are administered close together. The most common side effects that happen during or soon after a belimumab dose are nausea, diarrhoea, and fever.

Where is the study run from?
University College London Hospital (lead centre) and 14 other NHS hospitals in England (UK)

When is the study starting and how long is it expected to run for?
September 2016 to December 2020

Who is funding the study?
1. Versus Arthritis (formerly known as Arthritis Research UK)
2. GlaxoSmithKline foundation (UK)
3. University College London Biomedical Research Centre (UK)

Who is the main contact?
1. Ms Felecia Ikeji (public)
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2. Professor Michael Ehrenstein
m.ehrenstein@ucl.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-005543-14

Protocol serial number
32235

Study information

Scientific Title
Safety and efficacy of Belimumab After B cell depletion therapy in systemic LUPUS erythematosus

Acronym
BEAT LUPUS

Study objectives
This study aims to find out whether a drug called Belimumab when used after B cell depletion therapy is safe and effective in reducing systemic lupus erythematosus (lupus) disease activity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Hampstead Research Ethics Committee, 07/07/2016, ref: 16/LO/1024

Study design
Multicentre phase II randomised double blind placebo-controlled clinical trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Systemic lupus erythematosus

Interventions
Participants are randomised to one of two groups.

Intervention group: Patients will recieve Belimumab according to the standard dosage regime of infusions of 10mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter up until week 52.

Control group: Patients will receive the same volume of normal saline infusions (0.9% saline) at the same time points as the active treatment group.

In total the treatment period (Belimumab or placebo) will be 52 weeks, with 16 weeks of further follow up. Each patient will therefore be enrolled in the study for 68 weeks in total.

Intervention Type
Other

Primary outcome(s)
Anti dsDNA-antibody levels are measured using blood sample testing at week -4 (baseline) and 52 weeks.

Key secondary outcome(s))
Current secondary outcome measures as of 26/03/2019:
1. Anti-dsDNA antibody levels at 24 weeks.
2. Proportion of participants with any adverse events by 52 weeks.
3. Proportion of participants with any serious adverse events by 52 weeks.
4. Proportion of participants with any infections by 52 weeks.
5. Proportion of participants with a severe disease flare (defined as one BILAG A or two B flares) by 52 weeks.
6. Proportion of participants with a severe or a moderate disease flare (defined one BILAG B flare accompanied by an increase in concomitant lupus medication - glucocorticoids, Mycophenolate, Azathioprine, or Methotrexate) by 52 weeks.
7. Time to severe disease flare.
8. Proportion of participants with a severe disease flare by 24 weeks.
9. SLEDAI 2000 at 52 weeks.
10. Subject Global Assessment of Disease Activity (SGADA) at 52 weeks.
11. C3 levels at 52 weeks.
12. Immunoglobulin levels at 52 weeks.
13. Cumulative steroid dose from randomisation to 52 weeks.
14. Proportion of participants decreasing steroid dose at randomisation by 50% without experiencing a severe flare, or if below 10mg/day at randomisation reducing dose to 5mg/day or less at 52 weeks.
15. Lupus Quality of Life (Lupus QoL), SF-36 at 52 weeks
16. Average EQ-5D from randomisation to 52 weeks.
17. C-SSRS (Columbian Suicide Severity Rating Scale) to assess suicidality risk at 52 weeks.

Previous secondary outcome measures:
1. Anti-dsDNA antibody levels are measured using Blood sample testing at 24 and 68 weeks
2. Proportion of patients with any adverse events is measured by reviewing patient notes, blood sample testing, SLEDAI 2000 questionnaire, SLICC index and BILAG 2004 at week -4 , week 0, week 2 and every 4 weeks until week 68
3. Proportion of patients with any infections is measured by reviewing patient notes, blood sample testing, SLEDAI 2000 questionnaire, SLICC index, BILAG 2004” at week -4 , week 0, week 2 and every 4 weeks until week 68
4. Proportion of patients with any disease flare (defined as 1 BILAG A or 2 BILAG B flares) is measured by BILAG 2004 at week -4, week 0, week 2 and every 4 weeks until week 68
5. Time to disease flare (defined as 1 BILAG A or 2 BILAG B flares) is measured by BILAG 2004 at week -4 , week 0, week 2 and every 4 weeks until week 68
6. Proportion of patients with a BILAG A or 2 BILAG B flares is measured by BILAG 2004 at 24, 52

and 68 weeks
7. SLEDAI 2000 is measured by “SLEDAI 2000 at 52 weeks
8. Systemic lupus erythematosus disease activity is measured using Subject Global Assessment of Disease Activity (SGADA) at 52 weeks
9. C3 is measured by blood sample testing at week -4 , week 0, week 2 and every 4 weeks until week 68
10. Immunoglobulin levels are measured by blood sample testing at week -4 , week 0, week 2 and every 4 weeks until week 68
11. BAFF (measurement of RNA from whole blood) is measured by blood sample testing at week -4 , week 0, week 12, week 28, week 52 and week 68
12. Cumulative steroid dose during treatment from randomisation is measured by reviewing patient notes at week -4 , week 0, week 2 and every 4 weeks until week 68
13. Proportion of patients decreasing their baseline steroid dose by 50% without flaring from randomisation, or if below 10mg/day at baseline reducing steroid dose to 5mg/day or who discontinue glucocorticoids with stable disease is measured by reviewing patient notes at week -4 , week 0, week 2 and every 4 weeks until week 68
14.How systemic lupus erythematosus effects quality of participants life” is measured using Lupus Quality of Life (Lupus QoL), SF-36 and EQ5D questionnaires at week -4 , week 0, week 2 and every 4 weeks until week 68
15. Suicidality risk is measured using the C-SSRS (Columbia suicide severity rating scale) at week -4 , week 0, week 2 and every 4 weeks until week 68
16. Kinetics of B cell repopulation, B and T cell phenotype and function during repopulation using Flow Cytometry at week -4 , week 0, week 12, week 28, week 52 and week 68

Completion date
03/12/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 08/08/2018:
1. Aged between 18 and 75 years
2. Patients with 4 or more criteria for SLE according to the American College of Rheumatology (ACR) 1997 criteria or SLICC 2012 criteria or biopsy proven lupus nephritis with one additional supportive test on at least two occasions (positive ANA, anti-dsDNA antibodies or anti-Sm antibodies)
3. History of anti-dsDNA antibodies detectable at least once in the past 5 years prior to screening the patient on the study protocol (ELISA test is preferable for Anti dsDNA antibody testing)
4. Patients are due to be treated with the first infusion of this cycle of B cell depletion therapy (Rituximab) 4-8 weeks before randomisation (week 0, see participant timeline). Previous use of Rituximab is allowed prior to this cycle.
5. No contraindications to the use of Belimumab
6. Ability to provide informed consent

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1. Aged between 18 and 75 years
2. Patients with 4 or more criteria for SLE according to the American College of Rheumatology (ACR) 1997 criteria or SLICC 2012 criteria or biopsy proven lupus nephritis with one additional supportive test on at least two occasions (positive ANA, anti-dsDNA antibodies or anti-Sm antibodies)

3. History of anti-dsDNA antibodies detectable at least once in the past taken within one year of screening the patient on the study protocol (ELISA test should be used for Anti dsDNA antibody testing)
4. Patients have received the first infusion of this cycle of B cell depletion therapy (Rituximab) 4-6 weeks before randomisation (week 0, see participant timeline). Previous use of Rituximab is allowed
5. No contraindications to the use of Belimumab
6. Ability to provide informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
52

Key exclusion criteria
Current exclusion criteria as of 08/08/2018:
1. Severe “critical” SLE flare defined as BILAG A flare in CNS system or any SLE manifestation requiring more immunosuppression than allowed within the protocol in the physician's opinion
2. Pregnancy and/or Breast Feeding patients
3. At risk of pregnancy and unwilling to use an acceptable form of birth control contraception (see section 6.3.1.4)
4. Prior use of Belimumab, Atacicept or any biologic therapy (except Rituximab, but no other B cell depleting therapies)
5. Participation in any other interventional trial within the last 6 months
6. eGFR <30mls/min at screening
7. Active infections, including but not limited to:
7.1. Current or past infection with hepatitis B or C as defined by:
7.1.1. Hepatitis B surface antigen positive
7.1.2. Hepatitis B surface antibody positive and hepatitis B core antibody positive
7.1.3. Hepatitis C antibody positive
7.2. Historically positive HIV test or test positive at screening for HIV
7.3. Active TB.
8. Infection history:
8.1. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
8.2. Hospitalization for treatment of infection within 60 days of Day 0
8.3. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti parasitic agents) within 30 days of Day 0

9. Receipt of a live-attenuated vaccine within 3 months of week 0 (see participant timeline)
10. In the investigator's opinion, patients that are at high risk for infection (including but not limited to in dwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent severe urinary tract infection)
11. IgG levels below 4.0 g/L, IgA level < 10 mg/dL (IgG and IgA test must be performed no more than 10 days before study drug commenced for the second inclusion/exclusion criteria assessment at week 0)
12. Primary immunodeficiency
13. History of malignant neoplasm within the last 5 years
14. History of cervical dysplasia CIN Grade III cervical high risk human papillomavirus or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS) within the past 3 years. The patient will be eligible after the condition has resolved (e.g., follow-up HPV test is negative or cervical abnormality has been effectively treated >1 year ago)
15. Severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, pulmonary, cardiac, or neurological disease or, in the investigator's opinion, any other concomitant medical condition or significant abnormal laboratory value that places the participant at risk by participating in this study with the exception of diseases or conditions related to active SLE
16. Comorbidities currently requiring systemic corticosteroid therapy
17. Evidence of serious suicide risk including any history of suicidal behaviour in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgement, pose a significant risk
18. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
19. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0
20. White blood cells (WBC) <1.5 x 10(9)/L, Neutrophils <1 x 10(9)/L measured up to 10 days before week 0 (study drug commenced)
21. A history of major organ transplant or hematopoietic stem/cell/marrow transport or renal transplant.

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2. Pregnancy and/or Breast Feeding patients
3. At risk of pregnancy and unwilling to use an acceptable form of birth control contraception (see section 6.3.1.4)
4. Prior use of Belimumab, Atacicept or any biologic therapy (except Rituximab, but no other B cell depleting therapies)
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7.1.3. Hepatitis C antibody positive
7.2. Historically positive HIV test or test positive at screening for HIV
7.3. Active TB.
8. Infection history:
8.1. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
8.2. Hospitalization for treatment of infection within 60 days of Day 0

8.3. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti parasitic agents) within 60 days of Day 0
9. Receipt of a live-attenuated vaccine within 3 months of week 0 (see participant timeline)
10. In the investigator's opinion, patients that are at high risk for infection (including but not limited to in dwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent severe urinary tract infection)
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18. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
19. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0
20. White blood cells (WBC) <1.5 x 109/L, Neutrophils <1 x 109/L measured up to 10 days before week 0 (study drug commenced)

Date of first enrolment
16/02/2017

Date of final enrolment
31/03/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Hospital
235 Euston Road

London
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Study participating centre
Guy's Hospital
Great Maze Pond
London
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SE1 9RT

Study participating centre
Addenbrookes Hospital
Hills Road
Cambridge
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CB2 0QQ

Study participating centre
Manchester Royal Infirmary
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Hammersmith Hospital
Du Cane Road
White City
London
United Kingdom
W12 0HS

Study participating centre
Royal Free Hospital
Pond Street
London
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NW3 2QG

Study participating centre
The Royal London Hospital
Whitechapel Road
London
United Kingdom
E1 1BB

Study participating centre
Whipps Cross University Hospital
Whipps Cross Road
London
United Kingdom
E11 1NR

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham

United Kingdom
B15 2TH

Study participating centre
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Leicester General Hospital
Gwendolen Rd
Leicester
United Kingdom
LE5 4PW

Study participating centre
University Hospitals Coventry & Warwickshire
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CV2 2DX

Study participating centre
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Dudley Rd
Birmingham
United Kingdom
B18 7QH

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
GlaxoSmithKline foundation

Alternative Name(s)
GSK plc., GSK plc, Glaxo Wellcome plc, SmithKline Beecham plc, GlaxoSmithKline plc., GSK

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
University College London Biomedical Research Centre

Results and Publications

Individual participant data (IPD) sharing plan
Individual de-identified participant data that will underlie the results of the trial publication will be available from 6 months up to 36 months following the trial publication. This will be available to investigators whose proposed use of the data has been approved by an internal review committee identified for this purpose and whose aim is to achieve/analyse what is in the approved proposal. Proposals should be directed to cctu-enquiries@ucl.ac.uk. To gain access a Data Sharing Agreement (DSA) will be signed. Data will be shared by an appropriate secure facility and will be password protected. Participants have consented to sharing of pseudo-anonymised data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	26/10/2021	27/10/2021	Yes	No
Protocol article	protocol	16/12/2019	19/12/2019	Yes	No
Basic results		01/12/2021	03/12/2021	No	No
HRA research summary			28/06/2023	No	No
Other publications	Exploratory analysis	28/11/2022	10/02/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan	statistical analysis plan	16/07/2020	20/07/2020	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes