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STRATIFY lupus

A Phase IIIa randomised placebo-controlled biomarker enrichment trial: IgA2 anti-DNA antibodies as a biomarker of response to belimumab after rituximab in systemic lupus erythematosus

Version	V3.0
Date	9th September 2026
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CCTU 2023-457
Sponsor R&D ID #	160445
CTA #	CTA 20363/0495/001-0001
REC #	26/EE/0155
IRAS #	1013219

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General information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 6. It describes the STRATIFY lupus trial, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or modifications may be necessary. These will be circulated to registered investigators in the trial. Trial locations entering participants for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials. The SPIRIT Statement Explanation and Elaboration document can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

Sponsor

University College London (UCL) is the trial sponsor and has delegated responsibility for the overall management of the STRATIFY lupus trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director, CCTU at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor, London, WC1V 6LJ or via the Trial Team.

Funding

Funding for this research has been provided through a single grant awarded by Arthritis UK (Grant 23233) which includes a contribution from the Efficacy and Mechanism Evaluation Programme (EME), an MRC and NIHR partnership (NIHR169103).

Trial Registration

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN76569516.

Trial Administration

Please direct all queries to the STRATIFY lupus Trial Manager at UCL CCTU in the first instance; clinical queries will be passed to the Chief Investigator by the Trial Manager.

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Coordinating Site:
Comprehensive Clinical Trials Unit at UCL (UCL CCTU)
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Structured trial summary

Acronym or short title	STRATIFY lupus
Scientific Title	A Phase IIIa randomised placebo-controlled biomarker enrichment trial: IgA2 anti-DNA antibodies as a biomarker of response to belimumab after rituximab in systemic lupus erythematosus
CCTU Trial Adoption Group #	CCTU 2023-457
Sponsor R&D ID #	160445
CTA #	CTA 20363/0495/001-0001
EudraCT #	N/A
REC #	26/EE/0155
IRAS #	1013219
Primary Registry and Trial Identifying Number	ISRCTN: ISRCTN76569516
Date of Registration in Primary Registry	10-Aug-2026
Secondary Identifying Numbers	Arthritis UK Award Reference 23233 Efficacy and Mechanism Evaluation Programme (EME), an MRC and NIHR partnership (NIHR169103)
Source of Monetary Support	Arthritis UK Efficacy and Mechanism Evaluation Programme (EME), an MRC and NIHR partnership
Material Support	GSK
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Professor Michael Ehrenstein, University College London, 4th Floor, Room 418 5 University Street London WC1E 6JF Phone 020 3108 2153 Email: m.ehrenstein@ucl.ac.uk Dr Muhammad Shipa University College London, 4th Floor, Room 418 5 University Street London WC1E 6JF Email: m.shipa@ucl.ac.uk
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Systemic Lupus Erythematosus patients with active lupus and due to receive B cell depletion therapy as part of standard of care (SOC)
Intervention(s)	All eligible participants will be randomised to one of the following arms:

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	Arm A (active): Belimumab infusions of 10 mg/kg on Day 0, Week 2, Week 4, and at 4-week intervals thereafter until week 48. **Arm B (placebo):** Same volume of normal saline (sodium chloride 0.9%) infusions at the same time points as the active treatment group.
Key Inclusion and Exclusion Criteria	**Inclusion criteria:** 1. Aged between 16 and 75 years inclusive at screening. 2. Participants who meet the 2019 criteria for SLE according to the European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. 3. Positive serum IgA2 anti-dsDNA antibodies (≥12.5AU) at time of screening measured in the Rayne UCL laboratory*****. 4. Participants due to be treated with the first infusion of B cell depletion therapy (e.g. Rituximab) 4-8 weeks before randomisation (Day 0, see participant timeline) for active SLE. Previous use of Rituximab is allowed prior to this cycle. 5. No contraindications to the use of Belimumab. 6. Participants willing and able to provide informed consent. ****IgA2 results defined in the Rayne UCL laboratory*** **Exclusion criteria:** 1. Pregnant or planned pregnancy during the trial and/or breastfeeding. 2. Women of childbearing potential (WOCBP) unwilling or unable to use highly effective contraception or abstinence (as described in section 3.2.1) for the duration of the trial and for at least 4 months following the last dose of the study drug. 3. Prior use of any biologic/advanced therapy (except rituximab given as part of this trial after screening) less than 6 months before randomisation. 4. Participation in any other interventional trial within the last 6 months before randomisation. 5. eGFR <30mls/min at screening 6. Active infections, including but not limited to: i. Current or past infection with hepatitis B or C as defined by: A. Hepatitis B surface antigen positive

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	B. Hepatitis B surface antibody positive and hepatitis B core antibody positive C. Hepatitis C antibody positive ii. Historically positive HIV test or test positive at screening for HIV iii. Active TB. 7. Infection history:* i. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) ii. Hospitalization for treatment of infection within 30 days prior to randomisation 8. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 30 days prior to randomisation.* 9. Receipt of a live-attenuated vaccine within 3 months prior to randomisation.* 10. In the investigator's opinion, participants 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. Primary immunodeficiency. 12. History of malignant neoplasm within 5 years prior to randomisation except for basal cell carcinomas of the skin, squamous cell carcinomas of the skin, and carcinoma in situ of the cervix that have been completely excised and considered cured for > 2 years prior to screening. 13. 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 participant 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).

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	14. 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 except for diseases or conditions related to active SLE.* 15. Comorbidities not lupus related currently requiring systemic corticosteroid or immunosuppressant therapy. 16. Evidence of serious suicide risk including having any history of suicidal behaviour in the last 6 months and/or suicidal ideation in the last 2 months, or who in the investigator's judgement, pose a significant suicide risk. 17. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies. 18. IgG levels < 4.0 g/L or IgA level < 10 mg/dL tested no more than 10 days before randomisation.** 19. White blood cells (WBC) <1.5 x 10^9/L or Neutrophils <1 x 10^9/L measured no more than 10 days before randomisation.** 20. Current drug or alcohol abuse or dependence or a history of drug or alcohol abuse or dependence within a year prior to randomisation. *These participants may be re-screened once treated and the specified window has expired. **If participants fail to meet this exclusion criteria, they cannot be re-screened.
Study Type	This is a UK multicentre, randomised, double blind, parallel group placebo-controlled clinical trial.
Study setting	NHS Hospitals
Date of First Enrolment	November 2026
Target Sample Size	66
Trial Duration	51 Months
Primary Outcome(s)	Modified Major Clinical Response (MCR) at 52 weeks: Reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 2 (without including the IgG anti-dsDNA antibody component) and no increase in

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	immunosuppressant dose in the last 3 months before 52 weeks.
Key Secondary Outcomes	1) Modified Major Clinical Response (MCR) at 24 weeks: Reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 2 (without including the IgG anti-dsDNA antibody component). 2) Major Clinical Response (MCR) at 24 and 52 weeks: Reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 4. For the 52- week outcome: no increase in immunosuppressant in the last 3 months. 3) Time to first incidence of: a. severe BILAG-2004 A flare (severe flare: a BILAG-2004 A score due to items which are "new" or "worse"; or, in the renal or haematological systems, an A score due to items which didn't result in an A score last month). b. severe or moderate BILAG-2004 flares (moderate flare: 2 BILAG-2004 B scores due to items which are either "new" or "worse"; or, in the renal or haematological systems, B scores due to items which didn't result in a B score last month) accompanied by an increase in concomitant lupus medication: glucocorticoids, or immunosuppressant through to 24 and 52 weeks. c. severe or moderate BILAG-2004 flare (moderate flare: 2 BILAG-2004 B scores due to items which are either "new" or "worse"; or, in the renal or haematological systems, B scores due to items which didn't result in a B score last month). d. BILAG-2004 low disease activity with prednisolone i) ≤5mg/day (BILAG-2004 LDA-5) ii) ≤7.5mg/day (BILAG-2004 LDA-7.5), and stable dose of immunosuppressive drugs. 4) Time to achieve: a) BILAG-2004 low disease activity with prednisolone i) ≤5mg/day ii) ≤7.5mg/day and stable dose of immunosuppressive drugs. b) LLDAS. c) DORIS remission. 5) Proportion of patients at 24, 36 and 52 weeks in:

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	a) BILAG-2004 low disease activity with prednisolone i) ≤5mg/day ii) ≤7.5mg/day and stable dose of immunosuppressive drugs b) DORIS remission c) LLDAS 6) Cumulative steroid and immunosuppressant doses during treatment from randomisation to 52 weeks. 7) Lupus Quality of Life (LupusQoL), SF-36 and EQ5D at 52 weeks. 8) IgA2 anti-dsDNA antibody levels at 24 and 52 weeks. 9) Proportion of participants with any infectious serious adverse event through to week 52 of the trial. 10) Proportion of participants with any adverse events and proportion with any serious adverse events through to week 52 of the trial. 11) Total serum IgG levels at 52 weeks.
Ancillary studies	None

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Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

Protocol contributors

Name	Affiliation	Role
Professor Michael Ehrenstein	UCL	Chief Investigator, Professor of Rheumatology
Dr Muhammad Shipa	UCL	Co-applicant, Consultant Rheumatologist
Professor Caroline Gordon	University of Birmingham	Co-applicant, Emeritus Professor of Rheumatology
Professor Ben Parker	Manchester University NHS Foundation Trust	Co-applicant, Consultant Rheumatologist
Professor Nick Freemantle	UCL CCTU	Co-applicant, Professor of Clinical Epidemiology and Biostatistics, Director of UCL CCTU
Dr Chee-Seng Yee	Doncaster and Bassetlaw Hospitals NHS Trust	Co-applicant, Consultant Rheumatologist,
Felicia Ikeji	UCL CCTU	Co-applicant, Head of Clinical Trial Operations
Kashfia Chowdhury	UCL CCTU	Co-applicant, Principal Research Fellow, Medical Statistician
Eleanor Hawkins	Ufonia Ltd.	Co-applicant, PPI Lead

Role of trial sponsor and funders

Name	Affiliation	Role
University College London (UCL)	N/A	Regulatory Sponsor
UCL Comprehensive Clinical Trials Unit (CCTU)	UCL	UCL as the trial sponsor has delegated all sponsor duties to UCL CCTU. A Clinical Project Manager (CPM) will oversee the Trial Manager (TM) who will be responsible for the day-to-day management of the trial, identifying and providing support to the trial teams at all participating trial locations and coordinating centres. Responsibilities include securing arrangements to initiate, manage and finance the trial. CCTU staff will be involved in trial location set up including trial protocol and participant information development, ethics and regulatory submissions, case report form development and database construction, in collaboration with the STRATIFY lupus Trial Management Group.
Arthritis UK	Charity	Trial funder
The National Institute for Health and Care Research (NIHR)	UK Government organisation, funded by the	Trial funder

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	Department of Health and Social Care (DHSC)	
GSK	Pharmaceutical and biotechnology organisation	Marketing Authorisation holder of IMP, providing belimumab at no cost.

Sponsor Trial Team

Name	Affiliation	Role
Professor Michael Ehrenstein	UCL	Chief Investigator
Dr Muhammad Shipa	UCL	Principal Investigator UCLH
Professor Nick Freemantle	UCL CCTU	Director Comprehensive Clinical Trials Unit, Professor of Clinical Epidemiology and Biostatistics
Felicia Ikeji	UCL CCTU	Head of Clinical Trial Operations
Kashfia Chowdhury	UCL CCTU	Oversight statistician
Norin Ahmed	UCL CCTU	Trial statistician
Lee Webber	UCL CCTU	Clinical Project Manager
Olivia Mahoro	UCL CCTU	Trial Manager & Trial Management Group Facilitator
Katherine Chan	UCL CCTU	Data Manager

Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Michael Ehrenstein	UCL	TMG Chair, and Chief Investigator. Overall responsibility for the conduct of the trial, ensuring deliverables and expectations of the oversight group are met
Dr Muhammad Shipa	UCL	Co-applicant, Principal Investigator UCLH, Trial design, all aspects of trial/protocol development, costing, execution, analysis, biomarker studies
Professor Caroline Gordon	University of Birmingham	Co-applicant, Trial design, all aspects of trial/protocol development, analysis
Professor Ben Parker	Manchester University NHS Foundation Trust	Co-applicant Trial design, all aspects of trial/protocol development, analysis
Professor Nick Freemantle	UCL CCTU	Co-applicant, Director Comprehensive Clinical Trials Unit, Professor of Clinical Epidemiology and Biostatistics, providing expertise to trial design and deliverables
Dr Chee-Seng Yee	Doncaster and Bassetlaw Hospitals NHS Trust	Co-applicant, Principal Investigator Doncaster and Bassetlaw Hospitals, trial design, all aspects of trial/protocol development, analysis
Felicia Ikeji	UCL CCTU	Co-applicant, Head of Clinical Trial Operations providing oversight of

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		governance, trial conduct as per protocol, trial design, Quality Management in line with CCTU SOPs and prevailing legislation.
Kashfia Chowdhury	UCL CCTU	Co-applicant, Oversight statistician. Senior oversight and supervision of trial statistician in designing the statistical analysis plan (SAP), statistical analyses and statistical reports
Norin Ahmed	UCL CCTU	Trial statistician
Eleanor Hawkins	Ufonia Ltd.	Co-Applicant, PPI Lead
Claire Beesley	UCL	Rayne UCL laboratory Research Fellow, providing expertise on laboratory aspects
Lee Webber	UCL CCTU	Clinical Project Manager, providing oversight of governance, contracting budget management and oversight of trial delivery
Olivia Mahoro	UCL CCTU	Trial Manager & Trial Management Group Facilitator, providing the day-to-day management of the trial including the development of trial protocol and supporting participant documents, ethics and regulatory submissions, trial location set up and support to all participating trial locations.
Katherine Chan	UCL CCTU	Data Manager, responsibilities include the development of the CRF and Metadata design, Database testing, Data Management Plan, Data queries, Preparation of reports, data cleaning

Trial Steering Committee

Name	**Affiliation**	**Role**
Dr Peter Lanyon	Nottingham University Hospital NHS Trust	Independent Chair
Professor Lee Suan Teh	East Lancashire Hospitals	Independent clinician
Professor Vern Farewell	MRC Biostatistics Unit, Cambridge	Independent statistician
Professor Mike Ehrenstein	UCL	Non-independent, Chief Investigator
Claire Route	Lay person	PPI member
Sherron Alexander-Beddinfield	Lay person	PPI member

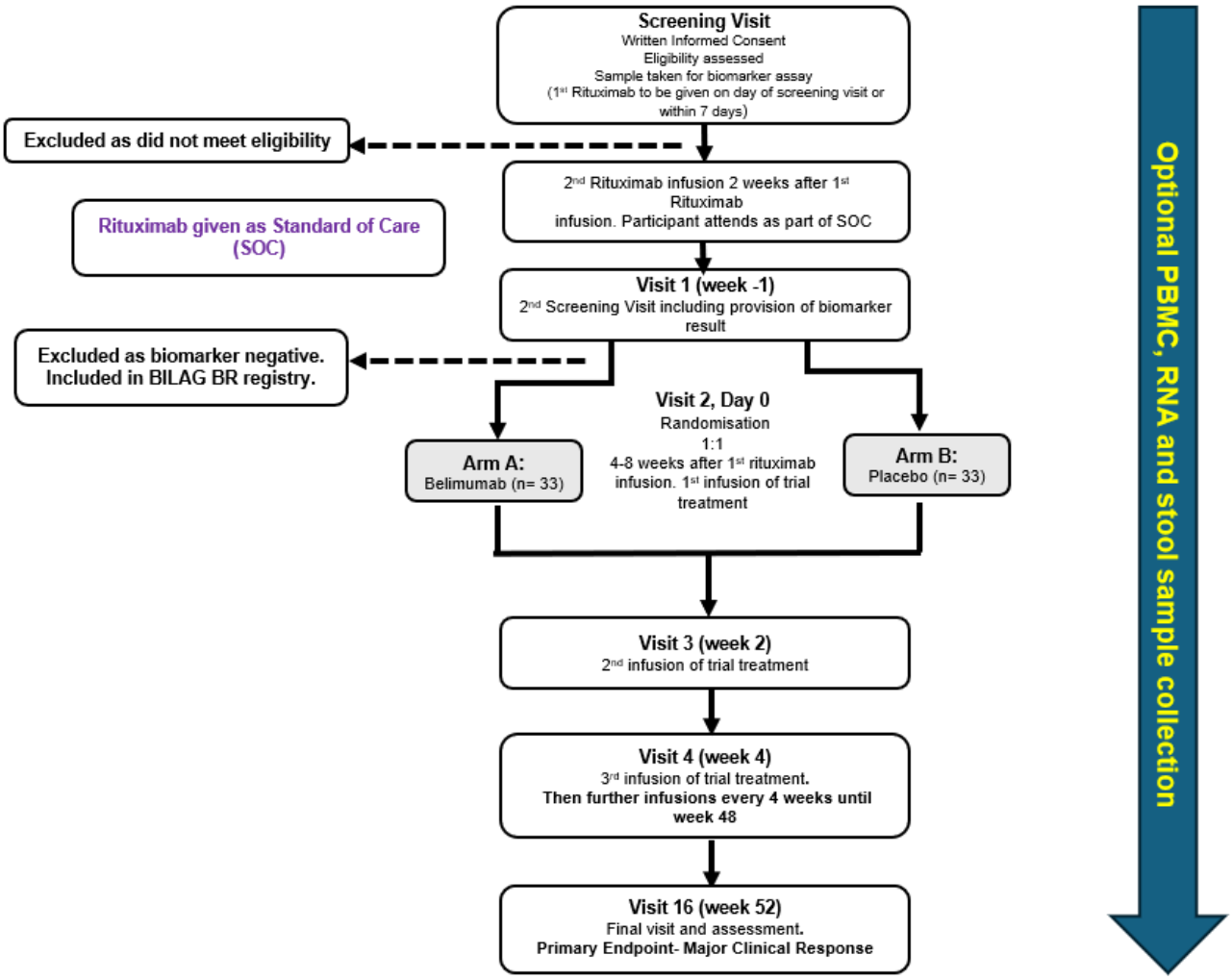
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Independent Data Monitoring Committee

Name	Affiliation	Role
Dr Bridget Griffiths	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Independent Chair
Raoul Mansukhani	London School of Hygiene & Tropical Medicine	Independent Statistician
Claire Riddell	Belfast Health and Social Care Trust	Independent Clinician
Dr Arvind Kaul	St. George's University Hospitals NHS Foundation Trust	Independent Clinician

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Trial Diagram



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Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BILAG-2004	British Isles Lupus Assessment Group disease activity index 2004
BILAG-2004 LDA-5	BILAG 2004 low disease activity with prednisolone dose ≤ 5mg/day
BILAG-2004 LDA-7.5	BILAG 2004 low disease activity with prednisolone dose ≤ 7.5mg/day
BCDT	B Cell Depletion Therapy
C3	Complement component 3
C4	Complement component 4
CA	Competent Authority
CCTU	Comprehensive Clinical Trials Unit at UCL
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRP	C-reactive protein
DSUR	Development Safety Update Report
DORIS	Definitions Of Remission In SLE
EC	Ethics Committee
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICH	International Conference for Harmonisation
ICF	Informed Consent Form
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
LLDAS	Lupus Low Disease Activity State
MedDRA	Medical Dictionary for Regulatory Activities
MCR	Major Clinical response
MHRA	Medicines and Healthcare products Regulatory Agency
mNCA	Model Agreement for Non-Commercial Research
NAE	Notifiable Adverse Event
NHS	National Health Service
NIMP	Non-Investigational Medicinal product
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QP	Qualified Person
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
TMF	Trial Master File
TMG	Trial Management Group
ToR	Terms of Reference

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TSC	Trial Steering Committee
UCL	University College London
WOCBP	Women of Childbearing Potential

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Glossary

Term	Definition
Autoantibody production	The production of proteins by a person's immune system which attack the person's own tissues.
B cell activating factor (BAFF)	Molecule which is an important physiological mediator of B cell homeostasis/survival.
B cell depletion therapy	Treatment which reduces the B cell population. In lupus, B cells produce autoantibodies which cause disease. For the purposes of this trial, Rituximab is the recommended form of B cell depletion therapy.
Belimumab	A humanised monoclonal antibody which inhibits the effect of B cell activating factor.
BILAG-2004 score	Scoring system used to assess disease activity in lupus. It is a validated organ-based disease activity instrument that has been developed in the UK for use in clinical studies and clinical trials. It demonstrates sensitivity to change and has been adopted in other trials.
BILAG-2004 low disease activity	All 9 systems in BILAG-2004 have scores of C, D, or E (no Grade A or B score).
DORIS remission	Refers to a state of minimal disease activity with minimal treatment. It is defined by the absence of clinical SLE disease activity (SLEDAI-2K score of 0 and Physician's Global Assessment <0.5), regardless of serology, with allowed use of antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable doses of immunosuppressants and biologics.
Hypogammaglobulinemia	A low level of immunoglobulin G (IgG) (IgG helps the body to fight infections). This could theoretically lead to an increased incidence of infection.
Interventional trials	Trial in which a treatment (intervention) is given to a group of participants to see whether this changes the course of the disease. Often, outcomes in this group are compared with a group with the same disease which had no intervention (or placebo).

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LLDAS	(1) SLE Disease Activity Index (SLEDAI)-2K ≤4, with no activity in major organ systems (renal, central nervous system (CNS), cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; (2) no new lupus disease activity compared with the previous assessment; (3) SLEDAI-2K physician global assessment (scale 0–3) ≤1; (4) a current prednisolone (or equivalent) dose ≤7.5 mg daily; and (5) well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.
Modified Major Clinical Response	Modified Major clinical response is defined as reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 2 (without including the IgG anti-dsDNA antibody component).
Major Clinical Response	Major clinical response is defined as reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 4.
Rituximab	A chimeric monoclonal antibody that depletes the B-cell population by targeting cells bearing the CD20 surface marker.
Standard of Care	The normal/conventional treatment which would be given for the disease.
Systemic Lupus Erythematosus (SLE)	A chronic autoimmune disease in which proteins produced by a person's immune system (B cells) attack their own tissues. This may affect multiple organs. The severity and pattern of organs affected may vary between affected patients.
Women of Childbearing Potential	A woman is considered of childbearing potential (WOCBP) i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement

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	therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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1 Background

1.1 Rationale

Systemic lupus erythematosus (SLE) is a heterogenous autoimmune disease associated with profound immune abnormalities and inflammation in different organs, such as the kidneys and skin that can cause reduced quality of life. It is one of the top ten causes of death in young women, with the worst outcomes in ethnic minorities[1,2]. Patients with SLE continue to rely on corticosteroids with all their associated risks and adverse outcomes. Immunosuppressive agents such as mycophenolate or azathioprine are frequently used, in part to minimise the use of corticosteroids, but a proportion of lupus patients have disease that is refractory to conventional therapies and are likely to have higher morbidity and mortality[3,4]. Because of high cost and modest efficacy, access to novel licensed therapies in England is highly restricted.

Considerable strides in the understanding of lupus pathogenesis have formed the bedrock of translational science for this disease and spearheaded the development of novel treatments. However, only a small proportion of lupus trials have been successful with a wide range of clinical responses. Active drugs have only increased response rates by between 10 and 20% even in those few positive trials, and coupled with high drug costs lead to restricted or no access to novel licensed therapies for patients with SLE in many countries including the U.K. One licensed targeted therapy (anifrolumab) is currently unavailable in the UK with the manufacturer having withdrawn its submission to NICE in 2022 as there was insufficient evidence that the therapy was cost-effective. (https://www.nice.org.uk/guidance/ta793), whereas, belimumab, which binds to a molecule (BAFF) that activates B cells and causes autoimmunity and was licensed in the UK in 2016, remains restricted in the UK to only those patients with high disease activity uncontrolled by conventional therapy (https://www.nice.org.uk/guidance/ta752).

A recent survey indicated that belimumab is not frequently used for the management of (even refractory) lupus nephritis in the UK[5] and the manufacturer of belimumab withdrew its submission to NICE for its use in lupus nephritis (https://www.nice.org.uk/guidance/ta806). Rituximab, which depletes B cells, remains the most frequently used targeted therapy in the UK for active lupus (including lupus nephritis)[5] and despite not being licensed for SLE is approved by NHS England (Rituximab-for-refractory-Systemic-Lupus-Erythematosus-in-adults-and-post-pubescent-children-2.pdf).

Disease heterogeneity in lupus exceeds that of most other multisystem diseases and likely contributes to the low overall efficacy in clinical trials. Extensive studies using molecular phenotyping have stratified lupus patients into several major groups, which could account for the wide variation in response to targeted therapies. Stratification of patients is likely to aid treatment selection and improve outcomes, given the immunopathological and clinical complexity of SLE combined with heterogenous response to therapy. Clinical trials in SLE have yet to stratify participants based upon molecular phenotyping which may demonstrate heightened benefit for a particular subgroup of patients. Selecting the right treatment for the right patient through precision medicine has been described by one commentator as a ‘quest for the holy grail’ for SLE patients[6].

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A substantial body of evidence implicates B cells in the pathogenesis of SLE and the B cell targeting therapy rituximab has been used extensively to treat SLE patients. Research into rituximab's mechanism of action revealed a surge in BAFF levels after B cell depletion[7], and several trials have tested the combination of rituximab and belimumab in participants with SLE. The academic led BEAT-lupus trial, which tested the effectiveness of two biologic therapies in combination: belimumab and rituximab for refractory disease, reported results that demonstrated the risk of severe lupus flares was reduced 3-fold in the belimumab group compared to placebo, both after rituximab[8]. In the CALIBRATE trial which recruited 43 participants with refractory lupus nephritis, rituximab was given with cyclophosphamide, and then half the patients were treated with belimumab[10].To compare outcomes between the BEAT-lupus and CALIBRATE trials researchers at University College London (UCL), Department of Rheumatology, performed a post-hoc modified intention to treat analysis of the CALIBRATE trial (originally only a per protocol analysis had been published) and the BEAT-lupus trial. The overall response rate in the CALIBRATE trial (complete and partial renal response: 74% - combination arm, 61% - rituximab arm) was higher than the BEAT-LUPUS trial (major clinical response: 48% - combination arm, 35% - rituximab arm). The definitions of response differed in the two trials which reflected the different patient populations.

The BEAT-Lupus trial demonstrated that participants treated with belimumab after rituximab had fewer severe disease flares during the trial compared to participants who received rituximab alone. But there was a wide variation in responsiveness with a modest non-significant difference (13%) in clinical response at 1 year between the combination and rituximab alone.

Using machine learning (a form of artificial intelligence) applied to data from blood samples taken during the BEAT-lupus trial, we identified baseline serum IgA2 anti-dsDNA antibody levels, measured using a simple (ELISA) assay, as a predictor (biomarker) of response to belimumab after rituximab[11]. In contrast, serum IgG anti-DNA antibodies, which is conventionally used to guide the use of belimumab had no predictive value. This predictive biomarker was confirmed by using serum samples (blinded) from the CALIBRATE trial testing the same combination. Combining data from both trials yielded an optimised cut-off value of 12.5AU. The difference in the proportion of responding patients between belimumab and rituximab combination compared to rituximab alone increased to 59% in patients with high levels of IgA2 anti-dsDNA antibodies from 14% in unselected patients. For the BEAT-lupus trial alone using ≥12.5 AUs at baseline as the cut point, the difference with respect to clinical response between the two arms of the trial was almost identical at 58%. These data suggest a striking relationship between baseline serum IgA2 anti-dsDNA antibodies and clinical response to belimumab after rituximab.

Serendipitously, the only biomarker identified that predicted response to belimumab after rituximab, IgA2 anti-dsDNA antibodies, is technically simple to assay using an ELISA and thus could be easily adopted into routine clinical practice. Moreover, the ELISA performs well in the laboratory with minimal variance when testing the same samples performed on different days by two different operators.

STRATIFY lupus is a placebo-controlled double blind clinical trial recruiting only biomarker positive participants (biomarker enrichment) to test the value of baseline serum IgA2 anti-dsDNA antibodies as a predictive biomarker potentially taking the guesswork out of when to

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use this combination therapy for maximum benefit. The objective of this trial is to test the hypothesis that participants with high baseline serum levels of this biomarker, will have a greater response to belimumab after rituximab compared to rituximab alone (which is NHS standard of care for patients that have failed other therapies). This multicentre (17 locations) trial will randomise 66 lupus participants with high serum IgA2 anti-dsDNA antibodies who are due to receive rituximab therapy as part of standard of care to receive combination belimumab after rituximab or placebo after rituximab. Rituximab remains the most frequently used advanced therapy for SLE in England and thus trial design will reflect real world practice. The primary endpoint will be major clinical response after 12 months. Tailoring therapies to those most likely to respond could be considered the holy grail of lupus therapy but has yet to be achieved. This proposed trial would be an exemplar of a biomarker enrichment trial to enable adoption of a precision medicine approach for lupus patients.

Sample collection during the trial to understand the mechanism of action of this combination, as well as further explore the role of IgA2 autoantibodies in the response to belimumab will enable continuation of the experimental medicine approach which has led to the design of this first-in-lupus landmark biomarker enrichment trial, challenging the conventional paradigm of drug development for SLE. Blood samples will be collected before and after trial treatment to analyse phenotypic and functional changes in B cells, and their interactions with other immune cells, in response to therapy. Stool samples (which are optional) will be collected by participants at home and be shipped to the Rayne UCL laboratory and are important since IgA2 is the major IgA subclass in the large bowel and preferentially target several microbiota compared to IgA1 in healthy individuals[11]. Stool samples will not only permit evaluation of IgA2 anti-dsDNA antibodies within the gut, but also identify bacteria bound by IgA2 and examine whether belimumab after rituximab affects microbial diversity and how these changes relate to impact the autoimmune response in SLE.

1.1.1 Explanation for choice of comparators

All biomarker positive participants will receive rituximab which aligns with real world practice for patients with severe SLE often refractory to conventional therapy and then be randomised to belimumab or placebo (plus standard of care) 4-8 weeks after the first infusion of rituximab. The trial is double blind to reduce bias. The choice of comparators is based on the BEAT-Lupus trial (ISRCTN 4787303) and the CALIBRATE trial (NCT02260934), testing the same combination belimumab after rituximab therapy but selecting participants most likely to respond (high serum IgA2 anti-dsDNA antibodies, at or above 12.5AU).

1.2 Objectives

1.2.1 Primary Objective

To determine whether clinical response, including prevention of disease flares through to 52 weeks, to belimumab after rituximab therapy is significantly superior to rituximab alone in lupus participants who are due to receive rituximab as part of their NHS standard of care and with high levels of serum IgA2 anti-dsDNA antibodies levels (≥12.5AU).

1.2.2 Secondary Objectives

To provide safety data, including occurrence of infections and hypogammaglobulinemia for this combination in biomarker positive participants during the 52- week trial duration.

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1.2.3 Mechanistic and Exploratory Objectives

Collection of blood (serum) and stool samples will help to understand the mechanism of action of this combination and further explore the role of IgA2 autoantibodies in the response to belimumab after rituximab. The collection of serum is mandatory for the trial because it is required to test the biomarker IgA2 anti-dsDNA antibody levels for the third inclusion criterion (see inclusion criteria). The collection of PBMC (peripheral blood mononuclear cells) and stool samples are optional. Because the majority of IgA2 is produced in the colon, stool samples will enable us to further understand the role of this subclass in lupus pathogenesis and response to therapy.

1.3 Trial Design

Stratify lupus is a UK Phase IIIa multicentre, randomised, placebo-controlled double-blind superiority 52-week biomarker enrichment trial investigating the efficacy of belimumab 4-8 weeks after rituximab compared to placebo, in patients who are positive for the biomarker, serum IgA2 anti-dsDNA antibodies. Rituximab will be given as Standard of Care (SOC) in participants with active lupus resistant to conventional therapy in accordance with NHS England Commissioning Policy[12] and administered according to local policy.

4-8 weeks after the first infusion of rituximab, participants will be randomised to receive belimumab or placebo. Intravenous administration of belimumab or placebo (normal saline, sodium chloride 0.9%) will be given from randomisation at the recommended standard dosage and intervals: 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for 48 weeks. The final assessment visit will occur at week 52.

1.4 Benefit Risk Assessment

Belimumab is a licensed therapy for SLE and is approved and used for patients whose disease is severe and often refractory to conventional therapy (NICE TA752). Belimumab, on its own, has been shown to be effective in randomised controlled trials. All trial participants will be recruited based on their physician's intention to treat with rituximab (i.e. standard of care). Belimumab after rituximab combination therapy does not confer any greater risk compared to rituximab alone[13]. Belimumab and rituximab are administered intravenously using standard protocols used in routine care to minimise any risks such as infusion reaction. The exclusion criteria are designed to minimise risk of these immune modulating treatments according to standard practice. Patients with active infection or low immunoglobulins will be excluded because of the risk of new or worsening infection. Participants will be randomised to receive belimumab or placebo 4-8 weeks after their first administration of rituximab. There will be a second screening visit, 1-week before randomisation principally to ensure that participants are not receiving treatment for a serious active infection. Patients with significant liver or renal impairment will be excluded.

Trial treatment will be administrated in a clinical setting by staff at participating trial locations, who are trained to administer IV infusions. In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. All participants will remain under clinical supervision for 3 hours after completion of each of the first 2 infusions and will be observed for any untoward safety signals. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. Beyond the first 2 infusions, participants will be monitored during and for an

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appropriate period after each infusion according to the trial location guidelines or standard operating procedure for IV infusions. The biomarker enrichment strategy of STRATIFY lupus is designed to maximise the benefit of the combination therapy, and it is anticipated this will not incur any additional risks to participants.

The table below summarises the risks, frequencies and mitigations of the Investigational Medicinal Product.

Name of IMP	Potential risk	Risk Frequency	Risk Management
Belimumab	Bacterial infections e.g. bronchitis, urinary tract infection	Very common	Potential participants will be screened in accordance with the study eligibility criteria in section 3, which will mitigate known potential risks associated with the IMP e.g. infection. Infections are very common in patients with lupus including due to standard of care treatment, and belimumab does not significantly increase the risk of infection. For the first two infusions of study treatment, participants will be closely monitored for at least 3 hours by their clinical team. This will mitigate potential risks related to reactions to the IMP e.g. hypersensitivity. This monitoring will continue during subsequent
	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection	Common	
	Leucopenia	Common	
	Hypersensitivity reactions	Common	
	Anaphylactic reaction	Uncommon	
	Delayed-type, non-acute hypersensitivity reactions	Rare	
	Depression	Common	
	Suicidal behaviour; suicidal ideation	Uncommon	
	Migraine	Common	
	Diarrhoea; nausea	Common	
	Injection site reactions; urticaria; rash	Common	
	Angioedema	Uncommon	
	Stevens-Johnson syndrome; toxic epidermal necrolysis	Not known	
	Pain in extremity	Common	
	Infusion or injection-related systemic reactions; pyrexia	Common	

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			infusions of study treatment. Adverse events will be recorded throughout the study, and serious adverse events will be reported in accordance with section 6. Participants may be withdrawn from study treatment due to an adverse/serious adverse event in accordance with section 4.2.4.

For risks and mitigations of tests and/or procedures above standard care that are being performed, these are associated with blood collection for safety and/or research purposes as well as IV administration of randomised study treatment. These risks are minimal and will be mitigated by trial location adherence to standard local practice and close monitoring of participants throughout their participation in the study.

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2 Selection of Trial locations/Investigators

2.1 Trial location Selection

The trial sponsor has overall responsibility for trial location and investigator selection and has delegated this role to UCL CCTU.

2.1.1 Study Setting

The trial will take place at up to approximately 17 specialist trial locations for patients with SLE across the UK. A list of the participating trial locations can be obtained upon request from the STRATIFY lupus Trial Manager at UCL CCTU.

2.1.2 Trial location/Investigator Eligibility Criteria

Once a trial location has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol and relevant Summary of Product Characteristics (SmPC(s)).

To participate in the STRATIFY lupus trial, investigators and trial locations must fulfil a set of criteria that have been agreed by the Sponsor and STRATIFY lupus Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

1. A named clinician is willing and appropriate to take Principal Investigator responsibility.
2. Suitably trained staff are available to recruit participants, enter data and collect samples.
3. The trial location should be able to store, prepare and dispense IMP appropriately.

2.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The Principal Investigator(s) must be willing to sign a Principal Investigator Declaration Schedule 6 of the Model Agreement for Non-Commercial Research (mNCA), to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their trial location is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications (provide an up-to-date CV), familiarity with the appropriate use of any investigational products and agreement to comply with the principles of GCP. The PI must agree to permit monitoring and audit as necessary at the trial location, and to maintain documented evidence of staff who have been delegated significant trial related duties.

2.1.2.2 Resourcing at the trial location

- The investigator should demonstrate potential for recruiting the required number of suitable participants within the agreed recruitment period.
- The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- The investigator should have available an adequate number of qualified staff and suitable facilities for the anticipated duration of the trial in order to conduct the trial properly and safely.

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- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational medicinal product and their trial-related duties and functions.
- The trial location should have sufficient data management resources to allow prompt data return to the CCTU (refer to the Data Management Plan for timelines).

2.2 Trial location approval and activation

Training will be performed prior to the activation of each trial location and will include all processes for the trial including but not limited to protocol training, data management procedures, procedures for handling of the investigational medicinal product, adverse event reporting procedures, procedures for laboratory samples and frequency and expectations for monitoring visits. A log of trial location initiation visit attendees will be kept in the TMF as a record of participants present. The visit may occur in person or via Videoconference as outlined in the QMMP.

The trial manager or delegate will notify the PI in writing of the plans for activation. Trial locations will not be permitted to recruit any participants until a letter for activation has been issued. On receipt of the signed mNCA (including the signed PI Declaration), completed delegation of responsibilities log and staff contact details, the Trial Manager or delegate will complete the green light process and issue written confirmation of trial location activation to the PI.

The trial location must conduct the trial in compliance with the protocol as agreed by the Sponsor and by the regulatory authority, and which was given favourable opinion by the Ethics Committee (EC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at CCTU.

A list of activated trial locations may be obtained from the Trial Manager.

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3 Selection of Participants

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of trial entry. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise a participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 Participant Inclusion Criteria

1. Aged between 16 and 75 years inclusive at screening.
2. Participants who meet the 2019 criteria for SLE according to the European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus.
3. Positive serum IgA2 anti-dsDNA antibodies (≥12.5AU) at time of screening measured in the Rayne UCL laboratory**. ***
4. Participants are due to be treated with the first infusion of B cell depletion therapy (e.g. Rituximab) 4-8 weeks before randomisation (Day 0, see participant timeline) for active SLE. Previous use of Rituximab is allowed prior to this cycle.
5. No contraindications to the use of Belimumab.
6. Participants willing and able to provide informed consent.

IgA2 results defined in the Rayne UCL laboratory

3.2 Participant Exclusion Criteria

1. Pregnant or planned pregnancy during the trial and/or breastfeeding.
2. Women of childbearing potential (WOCBP) are unwilling or unable to use highly effective contraception or abstinence (as described in section 3.2.1) for the duration of the trial and for at least 4 months following the last dose of the study drug.
3. Prior use of any biologic/advanced therapy (except rituximab given as part of this trial after screening) less than 6 months before randomisation.
4. Participation in any other interventional trial within the last 6 months before randomisation.
5. eGFR <30mls/min at screening
6. Active infections, including but not limited to:
    i. Current or past infection with hepatitis B or C as defined by:
        A. Hepatitis B surface antigen positive
        B. Hepatitis B surface antibody positive and hepatitis B core antibody positive
        C. Hepatitis C antibody positive
    ii. Historically positive HIV test or test positive at screening for HIV
    iii. Active TB
7. Infection history: *

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   i. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
   ii. Hospitalisation for treatment of infection within 30 days prior to randomisation

8. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 30 days prior to randomisation.*
9. Receipt of a live-attenuated vaccine within 3 months prior to randomisation.*
10. In the investigator's opinion, participants 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. Primary immunodeficiency.
12. History of malignant neoplasm within 5 years prior to randomisation except for basal cell carcinomas of the skin, squamous cell carcinomas of the skin, and carcinoma in situ of the cervix that have been completely excised and considered cured for > 2 years prior to screening.
13. 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) in the last 3 years prior to randomisation. The participant 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).
14. 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 except for diseases or conditions related to active SLE.*
15. Comorbidities not lupus related currently requiring systemic corticosteroid or immunosuppressant therapy.
16. Evidence of serious suicide risk including having any history of suicidal behaviour in the last 6 months and/or suicidal ideation in the last 2 months, or who in the investigator's judgement, pose a significant suicide risk.
17. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
18. IgG levels < 4.0 g/L or IgA level < 10 mg/dL tested no more than 10 days before randomisation.**
19. White blood cells (WBC) <1.5 x 10^9/L or Neutrophils <1.0 x 10^9/L measured no more than 10 days before randomisation.**
20. Current drug or alcohol abuse or dependence or a history of drug or alcohol abuse or dependence within a year prior to randomisation.

*These participants may be re-screened once treated and the specified window has expired.
**If participants fail to meet this exclusion criteria, they cannot be re-screened.

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3.2.1 Women of Childbearing Potential

A woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Female participants of childbearing potential must not become pregnant and agree to use a highly effective method of birth control whilst administering the IMP and for at least 4 months after last trial treatment. A highly effective method of birth control is defined as contraceptive methods that can achieve a failure rate of <1% per year when used consistently and correctly. Birth control measures should begin at screening and continue for the duration of trial treatment.

Discussions of contraception and chosen method(s) of contraception should be clearly documented in the participants medical notes during the Screening visit prior to randomisation and at each subsequent trial visit.

Any pregnancies that occur within 4 months of the last dose of trial treatment should be reported to UCL CCTU and followed up.

There is a limited amount of data from the use of Belimumab in pregnant women. No formal studies have been conducted, however Belimumab should not be used during pregnancy, therefore, pregnant women will be excluded from this trial.

It is unknown whether Belimumab is excreted in human milk or is absorbed systemically after ingestion. Because maternal antibodies (IgG) are excreted in breast milk, women that are breastfeeding will also be excluded from this trial.

Male participants do not have to use a highly effective contraceptive method or be sexually abstinent during the trial because paternal exposure to Belimumab in humans has not been associated with adverse pregnancy outcomes or foetal development.[14]

3.2.2 Birth Control Methods Considered as Highly effective

Highly effective contraceptive methods include:[15]

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - injectable
    - Implantable (*low user dependency)*

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- Intrauterine device (IUD) – (*low user dependency)*
- Intrauterine hormone-releasing system (IUS) – (*low user dependency)*
- Bilateral tubal occlusion – (*low user dependency)*
- Vasectomised male partner – (*low user dependency).* This is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence, defined as refraining from heterosexual intercourse (i.e., with male partner) when this is in line with the preferred and usual lifestyle of the participant, during the entire period of administering the trial treatment and for at least 4 months after last trial treatment.

Note: *Mycophenolate Mofetil (MMF) affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method*).

3.2.3 Unacceptable Birth Control Methods

Periodic abstinence (calendar, ovulation, symptothermal and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) **are not considered acceptable methods of contraception** in clinical trials. Female condom and male condom **should not** be used together.

Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action, double barrier methods such as a combination of condom with cap, diaphragm, or sponge with spermicide **are not considered highly effective** (i.e., have a failure rate of more than 1% per year).

3.2.4 Pregnancy Testing

Following written consent, all WOCBP will undergo a urine pregnancy test at the Screening Visit and at Visit 2, PRIOR to randomisation and 1st trial treatment. Thereafter, urine pregnancy tests will be performed at each subsequent visit (visit 3 to 15) and PRIOR to administration of the trial treatment. **The results of the urine pregnancy tests must be available prior to dispensing the IMP and should be clearly documented (either in a report or confirmation by the investigator or delegate) in the participants medical notes and in the trial database.**

A urine pregnancy test must be obtained from all WOCBP at Visit 16 (End of Trial).

3.3 Recruitment

A target of 66 participants will be recruited: 33 participants for each arm over a 24-month recruitment period. Details on the sample size calculation is provided in Section 8.1.

The participants will be recruited from up to 17 UK lupus trial locations which are part of the Translational Research Partnership (TRP) network, and/or who are part of the BILAG group which brings together the national specialist centres with expertise in lupus and are involved in the clinical management of large cohorts of lupus patients. University College London Hospitals NHS Foundation Trust (UCLH) will be the lead trial location. Four patient

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identification centres (PICs) in North London will be established and will refer all potentially eligible patients to UCLH.

Sixteen- and seventeen-year-olds will be recruited from paediatric /adolescent clinics.

Investigators will make use of the British Isles Lupus Assessment Group Biologics Register (BILAG-BR). This is a prospective register of patients starting biologics in the UK for SLE. About 70-100 patients with SLE are treated with rituximab each year and recruited to the BILAG-BR. Participants who are biomarker negative will be recruited to the BILAG-BR, but their follow up will not be part of STRATIFY lupus.

Potentially eligible patients will be approached by their treating clinician during routine or urgent standard of care outpatient appointments or when rituximab is being considered as part of their care in any hospital setting including inpatients.

The trial will be placed on the Sponsor website (CCTU) and will leverage sponsor specific social media platforms where applicable, to advertise the trial and provide regular updates on the trial progress.

The trial will be advertised at each trial location (using a REC/HRA approved trial poster) and potential participants will be provided with the trial team's contact details. Patient and Public Involvement (PPI) will support the design of recruitment materials. PPI representatives will also utilise their connections within the lupus community to aid recruitment.

Recruitment will be monitored regularly using Pre-screening/Screening logs to identify any barriers to recruitment, and to implement strategies where possible to overcome these barriers. Travel and subsistence costs will be offered to all participants and carers/legal representatives (at an agreed amount) for trial visits. Caring costs will also be considered for reimbursement.

Recruitment rates will be carefully monitored throughout the trial and any problems foreseen over the study set-up and recruitment period will be reported on a regular basis to the Trial Management Group, Trial Steering Committee and Arthritis UK to highlight any major challenges or obstacles impacting the trial timelines. Remedial action will be put in place as soon as these are identified.

3.4 Co-enrolment Guidance

Participants cannot be concurrently enrolled in any other interventional clinical trial or have received an investigational medicinal product for any indication within the last 3 months prior to randomisation and 1st trial treatment in this trial.

The Principal Investigator or delegated clinical Investigator(s) will be responsible for maintaining logs and ascertaining whether potential participants are currently taking part in another interventional clinical trial.

This trial will use screening and enrolment logs to track currently enrolled participants to ensure that each participant can only be enrolled once.

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3.5 Screening Procedures and Informed Consent

Potential participants and/or participant's carer/legal representative will be provided with a Participant Information Sheet (PIS) and will be given ample time to read it fully.

Following a discussion with a delegated medically qualified investigator/clinician, any questions will be satisfactorily answered. The discussion should include an assessment of the participant's capacity by a suitably experienced medically trained delegated member of the research team at the trial location, and if the participant is willing and wishes to participate, written informed consent will be obtained by a medically qualified clinician who is GCP trained, suitably qualified and experienced, and has been delegated this duty by the PI on the delegation log. A copy of a valid GCP certificate for individuals taking consent must be kept in the investigator site file (ISF).

It is the responsibility of the clinical trial research team at the trial location to ensure compliance with these requirements. Only research team members with suitable experience and training will take consent for such participants, and their experience and qualification to do this will be recorded in the STRATIFY lupus delegation log.

Consent to the use of their data and samples for future ethically approved research will also be sought.

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits, and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed.

It must be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment. Participation (or continued participation) in the trial must be refused if consent is not given.

Signed consent forms must be kept by the investigator and a copy given to the participant. The consent process should be documented in the participant's medical records. With the consent of the participant, a letter should be sent to the general practitioner informing him/her of the trial and the participant's involvement in it.

The PIS and ICF Forms will be approved by the Ethics Committee prior to their use.
For all participants, consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the PIS, submitted to REC as a modification, and approved by the REC prior to their use. The participant will be asked to sign an updated corresponding consent form.

A copy of the approved PIS and ICF forms are available from the STRATIFY lupus Trial Manager or delegate at CCTU trial team. **Once written informed consent** has been obtained, participants will undergo the screening procedures outlined in section 5.2 - Participant Timeline.

Re-screening of Participant (i.e. repeat of first screening visit above)

Where there is an abnormal test value (e.g., out of range blood results) at Screening, which in the opinion of the investigator may normalise, re-screening can be performed, and the

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participant should undergo a repeat of **ALL** the above screening procedures. A participant must be re-consented to the trial prior to any re-screening procedures being performed. Note this is not the 'second screen' which is detailed in the Participant Timeline (section 5.2).

History and Upon confirmation of eligibility, i.e., the participant **meets ALL the inclusion criteria and NONE of the exclusion criteria**, participants will be randomised and randomly allocated to one of the trial treatment arms (refer to section 4.0).

3.6 Trial Visits

Participants/parents and/or legal representatives will be asked to attend 17 clinic visits:

- Screening – Up to *7-days PRIOR to 1st Rituximab infusion.*
- Visit 1- second screening (specific exclusion criteria).
- Visit 2- Randomisation/ 1st infusion of trial medication.
- Visit 3-15 – Infusions every 4 weeks.
- Visit 16 - End of Trial.

Please refer to Section 5.2- Participant time for details of the trial assessments performed at each visit.

3.7 Serum and Optional samples collection

Mandatory serum samples will be collected from all participants to determine IgA2 anti-dsDNA antibody levels, which is required for the third inclusion criterion and constitutes secondary outcome measure 8 (refer to section 5.1.2).

For participants who have consented to the optional PBMC and RNA-Tempus tube sample collection, samples will be collected at trial location. Participants who have consented to optional stool sample collection will be provided with pre-paid packaging for the collection and shipment of stool samples to the Rayne UCL laboratory. PBMC, RNA-Tempus tube and stool sample collection will be done at specific timepoints during the trial, as detailed in the participant timeline.

All samples will be shipped to the Rayne UCL laboratory. Only the mandatory screening serum samples need to be shipped to UCL immediately (preferably on the day the serum sample is collected). Other samples (post-randomisation mandatory serum sample and any optional samples participants consent to) can be shipped at regular intervals. Please refer to the STRATIFY lupus Sample Management Plan for details on collection, processing and shipment of samples.

For details on all assessments performed at each visit, please refer to Section 5.2 for Participant Timeline.

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4 Trial treatments / Intervention

4.1 Introduction

In the active therapy arm, participants will receive Belimumab, according to the standard dosage regime. The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter until week 48.

The participants on the placebo arm will receive the same volume of Normal Saline infusions at the same time points as the active treatment group.

The treatment schedule consists of a 48-week double-blind treatment period with 4-weekly infusions (additional loading dose at 2 weeks), and a total of 14 infusions:

- Day 0.
- Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and Week 48 (End of Treatment).

There is an allowance of +/- 3 days for the 2- weekly scheduled treatment visits and +/- 7 days for the 4- weekly scheduled treatment visits.

4.1.1 Non-Investigational Medicinal Products (nIMPs)

Rituximab treatment will be administered to each participant regardless of randomisation group in line with current standard of care/local clinical practice given to participants with active SLE.

4.2 Arm A

4.2.1 Product

Belimumab with standard of care.

Belimumab is a human IgG1λ monoclonal antibody, produced in a mammalian cell line (NS0) by recombinant DNA technology. Belimumab will be manufactured and supplied by GSK; presented in Type 1 glass vials (20 mL per vial), sealed with a siliconised chlorobutyl rubber stopper and a flip-off aluminium seal containing 400 mg of powder for concentrate and distributed to participating trial locations by the sponsor approved 3rd party IMP distribution facility responsible for secondary labelling (in compliance with GMP, Annex 13), and QP release. Belimumab is administered intravenously by infusion and must be reconstituted and diluted before administration. After reconstitution, the solution contains 80mg belimumab per mL.

4.2.2 Regulatory Status

GlaxoSmithKline UK Limited is the holder of the Marketing authorisation. This licensed product is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive SLE with a high degree of disease activity despite standard therapy.

Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis.

4.2.3 Dispensing & Storage

At each participant's treatment visit belimumab will be dispensed by a delegated member of the trial pharmacy or research team, in accordance with the infusion codes assigned by the randomisation generated by Sealed Envelope Ltd, www.sealedenvelope.com. The Trial

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Pharmacist or unblinded designee should dispense the participant infusion to match the randomisation code. A list of infusion codes with the assigned treatment allocation will be provided to the pharmacy team (and the unblinded trial team member, if they will be preparing the belimumab) prior to activation of the trial location by the unblinded STRATIFY lupus Statistician.

The belimumab will be reconstituted and diluted and presented in blinded packaging to conceal the appearance, this must be carried out under aseptic conditions. The dose will be calculated based on the weight of the participant at the randomisation visit. The participant's weight will be measured at every trial visit and dose will only be adjusted if there is a >10% change in the participant's weight compared to the randomisation visit. No dose adjustment is recommended for underweight or obese participants.

Prescribing of trial medication should only be performed by members of the research team who have the necessary qualifications, training, and experience to do so and by those who have been delegated this task by the Principal Investigator (PI) as documented on the delegation log.

Once eligible participants are randomised (Randomisation, visit 2), the investigator or delegated member of the research team should complete the trial prescription and provide this to the individual delegated with the task of dispensing, reconstituting and diluting the belimumab.

Blinded infusion codes will be managed by the unblinded statistician at UCL CCTU.

The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for a total of 48 weeks.

Infusion will occur after the assessments and sample collection outlined in the Participant Timeline table are completed see section 5.2.

Belimumab will be administered IV over a minimum of 1 hour. The total time from reconstitution of belimumab to completion of infusion should not exceed 8 hours.

The infusion should be administered by investigators/trial location personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the participant develops an infusion reaction. Investigators/trial location personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor participants closely. In the event of a serious reaction, study agent administration must be discontinued immediately and the appropriate medical therapy administered.

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of each of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. Beyond the first 2 infusions, participants should be monitored during and for an appropriate period after each infusion according to local guidelines or standard operating procedure for IV infusions at the trial location.

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Infusion reactions occurred more frequently on the first two infusion days and tended to decrease in frequency with subsequent infusions. Delay in the onset of acute hypersensitivity reactions has been observed and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed. Therefore, participants should be monitored during and for an appropriate period after administration of Belimumab. Participants treated with Belimumab should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. For further information see the Belimumab SmPC. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

The relevant SmPC will be provided with the protocol.

Refer to Section 4.2.4 Dose modification/interruption and discontinuations.

Handling and management of the trial medication, including the additional dispensing labelling will be in accordance with GMP Annex 13 and subject to local pharmacy policy at each trial location.

Belimumab will be stored in its original carton to protect from light and in a refrigerator, between 2°C and 8°C during transportation and while at the local pharmacy.

This trial will follow a two-step activation process (partial activation), to allow provision of an initial supply of IMP. The maximum amount of IMP supplied, which will be considered as the "target stock level" will be based upon either the predicted or agreed recruitment figures or their storage capacity. Projected recruitment figures will be discussed during the trial location activation visit and prior to granting green light activation. Trial location re-supplies will be the responsibility of the investigator/pharmacy personnel and re-ordered as they reach crucial stock levels. Re-ordering will be managed by the unblinded pharmacy monitor or a delegate at UCL CCTU and expiry of medication will be managed by the STRATIFY lupus Trial Manager or delegate at UCL CCTU via GSK and the 3rd party IMP distribution facility.

Further details regarding distribution, labelling, administration, and storage of the IMP will be provided in the STRATIFY lupus IMP Management Plan.

4.2.4 Dose Modifications, Interruptions and Discontinuations

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may pause treatment, stop treatment early or be stopped trial participation early for any of the following reasons:

- IgG <3g/L.
- Unacceptable treatment toxicity or adverse event (based on CTCAE Version 6.0 2025)
- Inter-current illness that prevents further treatment.
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment.
- Withdrawal of consent for treatment by the participant or at the request of their legally authorised representative.
- If, in the opinion of the investigator or the IDMC, continuation in the study would be detrimental to the participant's well-being.
- Pregnancy. Female participants who become pregnant will be withdrawn from the trial

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treatment immediately. Any congenital abnormality or birth defect resulting from the pregnancy will be reported as a Serious Adverse Event. Women will be excluded if they are pregnant or lactating or of child-bearing potential (WCBP) unwilling to use highly effective contraception whilst receiving treatment and for at least 4 months after last trial treatment. A urine pregnancy test will be performed at each visit prior to drug administration.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled.

In all cases, the reason for withdrawal must be recorded on the case report form and in the participant's medical records. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. In cases of non-adherence to protocol, the remaining follow-up visits assessments should be performed for each participant, as far as possible. The investigator must make every effort to contact participants lost to follow up. Where participants have not fully adhered to the treatment regimen and/or visit schedule set out in the protocol, their data will be retained. The principles and procedures for analysing such data will be described in the Statistical Analysis plan.

Participants will be reviewed at least every 4 weeks from the time of randomisation.

4.3 Arm B

4.3.1 Products

Placebo with standard of care. Placebo used for this trial is Normal Saline solution (sodium chloride 0.9%) infusion.

4.3.2 Regulatory Status

Not applicable.

4.3.3 Dispensing & Storage

The participants on the placebo arm will receive the same volume of Normal Saline infusions at the same time points as the active treatment group. Dispensing will follow the same as that for Arm A **(refer to section 4.2.3)**. Trial locations will use Normal Saline supplied from their hospital stock. Storage will be in accordance with trial location local policy.

4.3.4 Dose Modifications, Interruptions and Discontinuations

Dose modifications, interruptions and discontinuations will follow the same as that for Arm A **(refer to section 4.2.4).**

4.4 Concomitant Care

This section applies to the care given after randomisation. Before randomisation including the period when rituximab is administered there is no limitation with respect to prednisolone or immunosuppressant dose, and intravenous cyclophosphamide can be administered with the rituximab if judged appropriate by the treating physician. However, no new immunosuppressant/immune targeting therapy (e.g. mycophenolate, azathioprine, methotrexate, voclosporin, tacrolimus, belimumab [except as part of this trial post

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randomisation]) can be initiated after screening. The maximum dose of mycophenolate after randomisation is 2g/day. The maximum dose of azathioprine after randomisation is 2mg/kg. The maximum dose of methotrexate allowed is 25mg/week. Only one of these three (azathioprine, methotrexate and mycophenolate) can be administered post randomisation. No other immunosuppressants (e.g. cyclophosphamide, tacrolimus, voclosporin) are allowed after randomisation except in the case of severe flare, see below. Reduction in corticosteroid to 5mg/day should take precedence over any reduction in immunosuppressant therapy and specifically do not reduce immunosuppressant medication in the last 3 months of the trial. Please contact the STRATIFY lupus team if further advice is required.

Background anti-malarial drugs are permitted but no new anti-malarials can be started after randomisation. Mepacrine is acceptable for skin problems resistant to Hydroxychloroquine, and both can be combined if this regime was started before randomisation. No change in dose of the anti-malarials can be made after randomisation except in the case of BILAG A or 2B flare.

Participants will be permitted to receive up to 20 mg prednisolone/day from randomisation and throughout. Prednisolone should be reduced to 7.5mg/day by 6 months post randomisation. A further reduction of the dose of prednisolone to 5mg/day is strongly encouraged by 36 weeks. Reduction below 5mg/day is allowed but not encouraged because of issues around endogenous production of steroids. Please note that participants are not allowed glucocorticoids via any route other than oral prednisolone during the study. This includes, but is not limited to, topical, intra-articular, intramuscular, and intravenous glucocorticoid administration. Exceptions are permitted only in the event of a moderate or severe flare, in accordance with the flare management guidance provided below. Guidance for the recommended prednisolone reducing regime will be provided to trial locations.

For participants with nephrotic range proteinuria and albumin levels of <20g/l, daily prophylactic low molecular weight heparin, dose adjusted according to renal function, is recommended to reduce the risk of thrombosis.

Treatment of hypogammaglobulinemia in participants with infectious AEs is permitted at the discretion of the investigator, in consultation with Chief Investigator.

The use of live-attenuated vaccines is prohibited during treatment with study medications and for 16 weeks after treatment. Use of COVID and influenza vaccines are permitted preferably before rituximab is administered but not after rituximab.

Measures to prevent and to treat osteoporosis are strongly encouraged during this trial. These measures may include vitamin D (up to 2000 IU/day), and bisphosphonates.

At the discretion of the investigator, participants may be treated with a cholesterol-lowering agent such as a statin.

ACE inhibitors and/or an angiotensin receptor blocker (ARB) may be started before but not after randomisation except in the case of a BILAG A or 2B flare (see below). Doses should be adjusted to achieve a targeted systolic blood pressure less than 130 mmHg. A combination of medications that may include an ACEi, ARB, calcium channel blocker, or beta-blocker may

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also be used if a single agent does not control systolic blood pressure adequately. Sodium glucose transport 2 (SGLT-2) inhibitors ('flozins') should not be commenced after randomisation (except in the case of flare, see below).

It is suggested that the participant refrain from using any herbal remedies. All herbal remedies should be recorded on the concomitant medications log.

Participants can continue to receive Hormone replacement therapy, but the dose should remain stable. Participants are advised not to stop HRT during the trial.

Participants **who flare with one BILAG A or two BILAG B scores** after randomisation will be permitted to receive other therapies designed to control the flare (e.g. voclosporin, tacrolimus) or increased prednisolone (including intravenous methylprednisolone/ above baseline dose of prednisolone / mycophenolate / azathioprine/ prednisolone / mycophenolate/ azathioprine / methotrexate) at the discretion of the treating physician (permission from UCL CCTU is not required) and can also continue with Belimumab or placebo at the discretion of their physician. One cycle of Rituximab can be used in the event of a BILAG A or 2 BILAG B flare after randomisation.

4.5 Overdose of Trial Medication

The trial drug will be administered during hospital stay by the research nurse under the supervision of the local Principal Investigator; overdose is therefore extremely unlikely. In the unlikely event of an overdose the participant will be treated as clinically appropriate, and this will be documented in the medical notes.

4.6 Unblinding

After the final database lock all participants will be unblinded to provide context and to aid their interpretation of the trial results. Treatment allocations will be shared with trial teams at this point for dissemination to the trial participants.

4.6.1 Emergency Unblinding

Unblinding may occur for any participant experiencing a medical emergency for which the clinical management will be facilitated by the unblinding of the participant's treatment allocation. All participants will be given a card with contact details for the trial team including emergency contact 24 hours a day, 7 days per week.

In the event of unblinding becoming necessary, the emergency contact will access the 24-hour web-based service offered by www.sealedenvelope.com. The Principal Investigator (PI) or delegate cannot overrule any decision made by a referring clinician. It is anticipated that in most instances; appropriate clinical management can proceed with the assumption that the participant has been treated with active IMP without needing to unblind the participant.

Detailed information regarding unblinding is provided in the STRATIFY lupus Randomisation and Unblinding Plan.

4.6.2 Unblinding for the Submission of SUSAR reports

All SAEs that are related to the trial medication (i.e., SARs) and are suspected to be unexpected i.e., SUSARs, need to be submitted to the regulatory agency within pre-specified timelines. When SAEs reports are received at the CCTU, if the event is recorded as being a SUSAR then the following procedure will be used to unblind the SUSAR to determine if the

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participant was receiving active trial medication, and therefore, that the SUSAR needs onward reporting to the regulatory agencies:

• A member of the CCTU trial SUSAR Reporting Team will unblind the participant's trial treatment allocation using the Sealed Envelope randomisation service.

• If the participant is revealed to the CCTU SUSAR Reporting team to be receiving active treatment, the CCTU trial SUSAR Reporting Team member will report the SUSAR on the Individual Case Safety Report (ICSR) Submissions portal available through the MHRA website and to the MHRA and REC as required.

• This information will not be forwarded to the trial team at the CCTU or at the trial location. It will be kept in a separate file by the CCTU SUSAR reporting team.

Detailed information regarding unblinding is provided in the STRATIFY lupus Randomisation and Unblinding Plan.

4.7 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant will stop treatment early or be stopped early for any of the following reasons:

- IgG <3g/L.
- Unacceptable treatment toxicity or adverse event.
- Inter-current illness that prevents further treatment.
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment.
- Withdrawal of consent for treatment by the participant or at the request of their legally authorised representative.
- If, in the opinion of the investigator or the IDMC, continuation in the study would be detrimental to the participant's well-being.
- Pregnancy. Female participants who become pregnant will be withdrawn from the trial treatment immediately. Any congenital abnormality or birth defect resulting from the pregnancy will be reported as a Serious Adverse Event. Women will be excluded if they are pregnant or lactating or of child-bearing potential (WOCBP) unwilling to use highly effective contraception whilst receiving treatment and for at least 4 months after last trial treatment. A urine pregnancy test will be performed at each visit prior to drug administration.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

It should be clear to the participant and recorded in the participant notes what aspect(s) of the trial the participant is discontinuing their participation. These could include:

- Early cessation of **further treatment.**
- Early cessation **from sample collections** (including optional research blood and stool samples where applicable).
- Early cessation **from questionnaires.**

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- Early cessation **from further trial follow-up.**
- Early cessation of **electronic health record use.**

Participants should always remain in the trial for the purpose of follow-up and data collection and analysis (unless the participant withdraws their consent from all stages of the trial). If a participant ceases follow-up early, refer to Section 5.4

Data on participants who stop follow-up early will be kept and included in analysis.

4.8 Accountability & Unused Trial Medication

The pharmacist at the trial location will be responsible for oversight of IMP supplies or may delegate this responsibility to the appropriately trained member of the Pharmacy Team.

Full IMP Accountability records will be maintained at the local pharmacy. Unused medication will be requested to be returned upon discontinuation of trial medication and destroyed or disposed of by the pharmacy on confirmation by the Sponsor. The CCTU will request copies of accountability logs and confirmation of destruction/disposal.

The CCTU will request copies of Accountability and Disposal Log to ensure IMP chain of custody.

Further details may be found in the STRATIFY lupus IMP Management Plan.

4.9 Compliance and Adherence

Belimumab/ placebo will be administered intravenously by trained medical staff; compliance, therefore, will be monitored by the medical staff at the trial locations and documented in the participant medical records and case report forms.

4.10 Eligibility Criteria for Individuals Performing the Interventions

Nursing staff, medical staff, and any other delegated members of the clinical trial team at the participating trial locations should have the appropriate qualifications to manage patients with SLE. Protocol-specific training will be provided to the research teams at the trial locations by the STRATIFY lupus Trial Manager or delegate at UCL CCTU prior to trial location activation or during the Initiation Visit. New staff who start work on the trial after trial location activation occurs, will be provided with protocol specific training prior to performing trial related procedures.

Each member of the trial team at each trial location will have their roles within the trial, as delegated by the PI, and documented on the trial location delegation log. Current CVs and GCP certificates of all individuals working on the trial will be collected by the STRATIFY lupus trial team at UCL CCTU to document their qualifications and relevant experience.

The IMP used for this trial will be administered at the trial locations by the research team. All participants enrolled in this trial must be available and willing to attend the visit time points during the duration of the trial.

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5 Assessments & Follow-Up

5.1 Outcomes

5.1.1 Primary Outcome(s)

Modified Major Clinical Response (MCR) at 52 weeks.

Modified MCR is defined as a reduction in *BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 2 (without including the IgG anti-dsDNA antibody component) and no increase in immunosuppressant dose in the last 3 months before 52 weeks.*

5.1.2 Secondary Outcomes

1) Modified Major Clinical Response (MCR) at 24 weeks.*
2) Major Clinical Response (MCR) at 24 and 52 weeks. For the 52- week outcome: no increase in immunosuppressant in the last 3 months.**
3) Time to first incidence of:
    a. severe BILAG-2004 A flare (severe flare: a BILAG-2004 A score due to items which are “new” or “worse”; or, in the renal or haematological systems, an A score due to items which didn’t result in an A score last month).
    b. severe or moderate BILAG-2004 flares (moderate flare: 2 BILAG-2004 B scores due to items which are either “new” or “worse”; or, in the renal or haematological systems, B scores due to items which didn’t result in a B score last month) accompanied by an increase in concomitant lupus medication: glucocorticoids, or immunosuppressant through to 24 and 52 weeks.
    c. severe or moderate BILAG-2004 flare (moderate flare: 2 BILAG-2004 B scores due to items which are either “new” or “worse”; or, in the renal or haematological systems, B scores due to items which didn’t result in a B score last month).
    d. BILAG-2004 low disease activity with prednisolone i) ≤5mg/day (BILAG-2004 LDA-5) ii) ≤7.5mg/day (BILAG-2004 LDA-7.5), and stable dose of immunosuppressive drugs.
4) Time to achieve:
    a) BILAG-2004 low disease activity with prednisolone i) ≤5mg/day ii) ≤7.5mg/day and stable dose of immunosuppressive drugs.
    b) LLDAS.
    c) DORIS remission.
5) Proportion of patients at 24, 36 and 52 weeks in:
    a. BILAG-2004 low disease activity with prednisolone i) ≤5mg/day ii) ≤7.5mg/day and stable dose of immunosuppressive drugs.
    b. DORIS remission.
    c. LLDAS.
6) Cumulative steroid and immunosuppressant doses during treatment from randomisation to 52 weeks.
7) Lupus Quality of Life (LupusQoL), SF-36 and EQ5D at 52 weeks.
8) IgA2 anti-dsDNA antibody levels at 24 and 52 weeks.

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9) Proportion of participants with any infectious serious adverse event through to week 52 of the trial.
10) Proportion of participants with any adverse events and proportion with any serious adverse events through to week 52 of the trial.
11) Total serum IgG levels at 52 weeks.

* Defined as a reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤ 2 (without including the IgG anti-dsDNA antibody component).

** Defined as a reduction in BILAG–2004 (British Isles lupus assessment group-2004) index A/B scores to BILAG–2004 C/D or remain E in all domains, a reduction in steroid dose to ≤7.5mg daily and a modified SLEDAI (Systemic lupus erythematosus disease activity index 2000) –2K score ≤4.

5.1.3 **Mechanistic Exploratory outcomes**

1. B cell phenotype, repertoire diversity and function including interactions with other immune cells during the trial and their relationship with clinical response.
2. Total serum IgG anti-dsDNA antibody levels at 24 and 52 weeks.
3. IgG, IgA1 and IgA2 lupus related autoantibody levels during the trial and their relationship with clinical response.
4. The gut microbiome signature and its relationship with immune phenotypic changes and clinical response.

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5.2 Participant Timeline

Assessments/study period	Screening	1st RTX	2nd RTX	2nd Screening	Trial Treatment period (Visit 2-15)														EoT	Severe lupus flare and/or Participant withdrawals[8]
Visit number	**0**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Day/Week	**Up to 7 days PRIOR to 1st RTX**	**4-8 weeks PRIOR to randomisation**	**SoC**	**Week -1**	**Day 0 Randomisation/ 1st infusion of trial treatment**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	
Visit window (days)				**+/-3**		**+/-3**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	
Informed Consent	x																			
Inclusion / Exclusion Criteria	x			x	x															
Past medical/surgical History	x			x																
Demographic data	x																			
Concomitant medication review	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (BP, HR, RR), urine dipstick	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine Pregnancy	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Criteria for SLE diagnosis	x																			
Review of immunosuppressive drugs for inclusion criteria	x				x															
History/physical examination	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SLEDAI 2000	x				x				x			x			x				x	x

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Assessments/study period	Screening	1st RTX	2nd RTX	2nd Screening	Trial Treatment period (Visit 2-15)														EoT	Severe lupus flare and/or Participant withdrawals[8]
Visit number	0			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Day/Week	Up to 7 days PRIOR to 1st RTX	4-8 weeks PRIOR to randomisation	SoC	Week -1	Day 0 Randomisation/ 1st infusion of trial treatment	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Visit window (days)				+/-3		+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	
BILAG 2004	x				x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physician's Global Assessment (PGA)	x				x				x			x			x				x	x
LupusQoL	x				x							x							x	x
SF-36	x				x							x							x	x
EQ5D	x				x							x							x	x
SLICC index	x																			
Immunoglobulins[1] (total IgM, IgG, IgA)[2]	x			x								x							x	x
Serum sample for IgA2 anti-dsDNA antibodies[3]	x				x				x			x			x				x	x
RNA & PBMC samples[4]	x				x							x							x	x
Stool sample[4]	x				x							x							x	x
ANA, ENA	x																			
FBC, ESR, CRP, U&E, LFTs	x			x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
PCR/ACR[5]	x				x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
IgG anti-dsDNA[6]	x				x				x			x			x				x	x
CD-19	x				x				x			x							x	x

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Assessments/study period	Screening	1st RTX	2nd RTX	2nd Screening	Trial Treatment period (Visit 2-15)														EoT	Severe lupus flare and/or Participant withdrawals[8]
Visit number	**0**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Day/Week	**Up to 7 days PRIOR to 1st RTX**	**4-8 weeks PRIOR to randomisation**	**SoC**	**Week -1**	**Day 0 Randomisation/ 1st infusion of trial treatment**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	
Visit window (days)				**+/-3**		**+/-3**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	
C3	x				x				x			x			x				x	x
C4	x				x				x			x			x				x	x
Rituximab infusion[7]		x	x																	
Randomisation					x															
Dispense and administer trial treatment (Placebo or Belimumab)					x	x	x	x	x	x	x	x	x	x	x	x	x	x		
AE review	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAE review	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[1]The week -1 results must be available **BEFORE** study drug administered and within 10 days of Day 0 (randomisation).
[2]Total IgG is measured for safety.
[3]Serum samples to Rayne UCL lab for IgA2 anti-dsDNA antibody testing. **Only the screening visit serum sample needs to be shipped on the day of collection to the Rayne UCL lab for biomarker testing.** Other samples can be shipped at regular intervals as detailed in the STRATIFY lupus Sample Management Plan.
[4]Stool, RNA tempus tube and PMBC samples (optional for trial locations that have been granted permission PRIOR to trial location activation). Please see Sample Management Plan for information about shipment of samples to the Rayne UCL laboratory.
[5]Urine PCR to be done if the protein dipstick shows 1+ or more. If PCR is not available trial locations can choose to perform ACR. The test chosen **MUST** remain the test of choice for the trial location throughout the duration of the trial. Note that if white cells are detected as well as protein on dipstick please send for culture in addition to PCR to ensure safety of participant (and assist with attribution to disease: document if white cell count meets criteria for urinary sediment in BILAG renal assessment if NO infection).
[6]IgG anti-dsDNA is used in SLEDAI-2000 calculations.
[7]Rituximab Infusion – Standard of Care as per NHS Commissioning policy.

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[8] Assessments to be performed at point of participant withdrawal or/and when severe lupus flares (BILAG A, or 2Bs that require change in immunosuppressive/increased glucocorticoid treatment) are reported.

Trial visit window:
Allowance of +/ -3 days for 2-weekly scheduled treatment visits.
Allowance of +/ -7 days for 4-weekly scheduled treatment visit.
EoT= End of Trial, Visit 16.

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5.3 Participant Transfers

If a participant moves from the area, every effort should be made for them to be seen at another participating trial location. A copy of the participant's CRFs should be provided to the new trial location, and the participant will need to sign a new consent form. Once this has been done, the new trial location will take over responsibility for the participant; until this has been completed, responsibility for the participant lies with the original trial location.

5.4 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should always be followed up providing they are willing, that is, they should be encouraged to not leave the whole trial; if they do not wish to remain on trial follow-up, however, their decision must be respected, and the participant will be withdrawn from the trial completely. The CCTU should be informed of this in writing using the appropriate documentation. Participants stopping early may have a negative impact on trial data integrity and the ability to reach the stated endpoints.

Data already collected during the participant's participation in the trial will be kept for analysis according to the intention-to-treat principle for all participants who stop follow up early. Any optional consent e.g. future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion).

Participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial.

Participants who stop trial follow-up early will not be replaced.

(See also Section 4.7 Protocol discontinuation).

5.5 Loss to Follow-up

If a participant is no longer contactable and has missed at least one follow-up visit within the protocol defined visit window, then staff at the trial locations should attempt to contact the participant at least three times via two different methods of contact (i.e., telephone and letter) before they are declared as lost to follow-up.

Efforts will be made to minimise loss to follow-up, such as tracing participants via their NHS number using NHS Digital records (Spine) (where they might have changed their GP) which supports the IT infrastructure for health and social care in England once approvals for access have been granted. Consent for this will be sought prior to the participant entering the trial.

5.6 Completion of Protocol Follow-Up

Participants will complete protocol follow up upon the completion of the final visit CRF.

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6 Safety reporting

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 6.1** lists definitions, **Section 6.3** gives details of the investigator responsibilities and **Section 6.3.2.2** provides information on CCTU responsibilities.

6.1 Definitions

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial.

Table 1: Definitions

Adverse Event (AE)	Any untoward medical occurrence or effect in a participant treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature, specificity or severity of which **is not consistent** with the known potentially expected events associated with the applicable trial treatment as detailed in the Reference Safety Information. The event is evaluated as having at least a reasonable possibility for a causal relationship to a trial treatment **and** is unexpected for that trial treatment.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • is another important medical condition***
* The term life threatening here refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g., a silent myocardial infarction). ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE. *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life threatening or do not result in death or hospitalisation but may	

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jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above (e.g., a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation, or development of drug dependency).

6.1.1 Medicinal Products

An investigational medicinal product is defined as the tested investigational medicinal product and the comparators used in the study (see section 4 of this protocol).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

6.1.2 Adverse Events

Adverse events include:

- an exacerbation (i.e., increase in the frequency or intensity) of a pre-existing illness, episodic event or symptom (initially recorded at the screening and baseline visit, prior to 1st dose of trial treatment), that is detected after trial drug administration/intervention.
- occurrence of a new illness, episodic event or symptom, that is detected after trial drug administration/intervention.

Adverse events that do NOT need to be reported:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event.
- Pre-existing disease or a condition present before treatment that does not worsen.
- Hospitalisation where no untoward or unintended response has occurred e.g., elective cosmetic surgery.
- Overdose of medication without signs or symptoms.
- Any new symptoms recorded on the BILAG 2004 Index Form which are related to SLE.

Adverse reactions potentially related to treatment

Infusion reactions:

Serious reactions may affect up to 1 in 100 people who receive Belimumab. Hypersensitivity reactions can be severe and can cause death. Symptoms may include nausea, chills, rhinitis, urticaria, hot flush, hypertension, rash, pyrexia, pruritus, throat irritation and hypotension.

Infections and vaccinations:

All participants will be warned about infection risk and to be vigilant for the signs of infection. Participants will be screened for chronic chest disease, viral hepatitis and HIV prior to trial entry and participants with chronic infection including opportunistic and herpes zoster will be

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excluded. It will be recommended that all participants have an annual influenza vaccination before and during the trial and confirmed that a pneumococcal vaccination has been given before randomisation, as per national guidelines for immunosuppressed patients. If COVID vaccination is considered appropriate, it is recommended to be given at least 2 weeks before rituximab but do not delay the rituximab infusion if the lupus disease is active. A clinical assessment to exclude current infection will also be performed prior to each infusion and at each 4-weekly assessment.

PML:
Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including Belimumab. A diagnosis of PML should be considered in any participant presenting with new-onset or deteriorating neurological signs and symptoms. The participant should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, the study agent should be discontinued, and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the UCL CCTU and the study drug suspended. If confirmed, the participant should cease trial treatment permanently.

Malignancy:
Although there is no evidence to date for an increased risk with Belimumab treatment, the possibility of immunosuppression resulting in an increased risk of malignancy cannot be excluded. Therefore, the protocol will exclude subjects who have had a prior malignancy within the last 5 years. During the trial, subjects will be questioned at all study visits about adverse events and results recorded in the eCRF. Examinations and laboratory evaluations will be performed routinely and the results, including markers of potential immunosuppression, will be reported to the investigators.

6.2 Pregnancy

From the time of consent, all pregnancies and suspected pregnancies that occur in female participants must be reported to UCL CCTU immediately of the trial location becoming aware using the notification and follow-up of pregnancy form.

Before any additional outcome of pregnancy or pregnancy complications can be reported to UCL CCTU, pregnant female participants must be given a copy of the trial pregnancy monitoring information sheet and asked to complete a pregnancy monitoring informed consent form for follow-up in pregnancy. The process should follow GCP, and the processes used to obtain consent for the clinical trial.

Outcomes should be reported to UCL CCTU no later than 10 months after the initial report. Any complications of pregnancy including miscarriage, congenital abnormality or birth defect resulting from the pregnancy must be reported as an SAE to UCL CCTU, within the timelines outlined in section 6.3.2.1.

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6.3 Investigator responsibilities

All non-serious AEs and ARs, whether expected or not, should be recorded in the participant's medical notes and reported to CCTU (via the trial database) within 5 working days. SAEs and SARs should be notified to CCTU immediately and no later than 24 hours after the staff at the trial location becomes aware of the event.

6.3.1 Investigator Assessment

6.3.1.1 Seriousness

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' then an SAE form must be completed and CCTU (or delegated body) notified immediately (within 24 hours).

6.3.1.2 Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in the Common Terminology Criteria for Adverse Events (CTCAE) Version 6.0 (2025).

Grades for AEs and ARs according to the CTCAE are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade 3: Severe or medically significant but not life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE or AR.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

Where no specific grading criteria exist for an event, the event should be graded according to the CTCAE general guidelines outlined above.

6.3.1.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2. There are two categories: related and unrelated. If the causality assessment is unrelated, the event is classified as an SAE. If the causality is assessed as related, then the event is classified as an SAR.

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Table 2: Assigning Type of SAE Through Causality

Relationship	Description	Event type
Related	A causal relationship between an IMP/investigational treatment and an adverse event is at least a **reasonable possibility**, i.e., the relationship cannot be ruled out	SAR
Not related	There is **no reasonable possibility** of a causal relationship between an IMP/investigational treatment and an adverse event	Unrelated SAE

If an SAE is considered to be related to trial treatment, and treatment is discontinued or interrupted, refer to the relevant Dose Modifications, Interruptions and Discontinuations sections of the protocol.

6.3.1.4 Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), the sponsor will assess the expectedness of the event. If information of expectedness is provided by the investigator this should be taken into consideration by the sponsor. An unexpected adverse reaction is one not previously reported in the current and approved version of the Reference Safety Information (the SmPC) for the trial, or one that is more frequently reported or more severe than previously reported.

6.3.1.5 Reference Safety Information (RSI)

The Reference Safety Information (RSI) for the STRATIFY lupus trial is Section 4.8 of the Belimumab (Benlysta) SmPC, for a list of expected toxicities associated with the active therapy being used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA reporting guidelines apply (see Notifications sections of the protocol).

6.3.2 Notifications

6.3.2.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs immediately after staff at the trial location become aware of the event (in no circumstances should this notification take longer than 24 hours).

Investigators should notify CCTU of any SAEs occurring from the time of consent until 30 days after the last protocol treatment administration, including SARs and SUSARs. From this point forward the trial location will not actively monitor SAEs but will notify the CCTU of any SARs and SUSARs if they become aware of them until trial closure.

Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

- The SAE eCRF must be completed by the staff at the trial location named on the delegation with this responsibility assigned by the PI. The form should be reviewed and electronically signed off by the Investigator (listed on the delegation log) responsible for the participant's care with attention paid to the grading and causality of the event. The responsible investigator should check the SAE form at the earliest

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opportunity, make any changes necessary and sign. Systems should be in place at the trial location to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the primary event term or outcome with sufficient information on the event to confirm seriousness, an identifiable coded participant, i.e., participant trial number, name of reporting principal investigator (PI) or by the staff at the trial location named on the delegation with this responsibility assigned by the PI. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

- Follow-up: Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. If there are ongoing SAEs at the study end this should be discussed with TMG. Follow-up SAE forms (clearly marked as follow-up) should be completed and sent to CCTU as further information becomes available. Additional information and/or copies of test results etc may be provided separately. The participant must be identified by trial number, partial date of birth where applicable. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.
- Staff should follow their institution's procedure for local notification requirements.

SAE REPORTING
Within 24 hours of investigator becoming aware of an SAE:
The SAE must be entered on to the sponsor's central database and the trial team at CCTU notified at:

cctu.STRATIFYlupus@ucl.ac.uk.

Where the central database is not available (e.g., system updates, system failure), a paper version of the SAE form (pCRF) will be provided to trial locations. The pCRF SAE must then be scanned and sent by encrypted email to the trial team at CCTU at: cctu.STRATIFYlupus@ucl.ac.uk

6.3.2.2 CCTU responsibilities

The sponsor Independent Safety Review Team (ISRT) will review, and complete expectedness assessments of SARs categorised by the local research teams at trial locations **as related to the intervention** against the RSI for the active treatment or comparator.

The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

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CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA). Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of CCTU becoming aware of the event; other SUSARs must be reported to the MHRA within 15 days.

CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

In the UK, an end of study declaration and final study report will be submitted to the REC.

A Development Safety Update Report (DSUR) will be submitted to the MHRA within 60 days of the international birth date of the trial and annually until the trial is declared ended.

6.3.2.3 Urgent Safety Measures (USMs)

The CCTU or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.

In the UK if any urgent safety measures are taken, the CCTU shall give written notice to the MHRA no later than 3 calendar days from taking any USMs, via the Integrated Research Application System (IRAS) of the measures taken and the circumstances giving rise to those measures, according to the relevant CCTU SOP.

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7 Quality Assurance & Control

7.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the STRATIFY lupus trial are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; benefit risk of the trial (see Section 1.4) and other considerations.

According to the MHRA Risk Assessment, this trial is defined as risk category A (i.e., no higher than that of standard medical care).

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

The STRATIFY lupus Risk Assessment has been reviewed by the CCTU's Quality Management Group (QMG).

7.2 Central Monitoring at CCTU

CCTU staff will review data and other information provided by investigators to identify trends, outliers, anomalies, protocol deviations and inconsistencies. The frequency and type of central monitoring will be detailed in the STRATIFY lupus Quality Management and Monitoring Plan (QMMP).

7.3 Monitoring

The frequency, type and intensity of routine on-site monitoring and the requirements for triggered on-site monitoring will be detailed in the STRATIFY lupus QMMP, including any provision for remote or self-monitoring. The QMMP will detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial inspection at a trial location by any regulatory authority UCL CCTU must be notified as soon as possible.

7.3.1 Direct access to Participant Records

Participating investigators must agree to allow trial-related monitoring, including audits, EC review and regulatory inspections, by providing access to source data and other documents as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

7.3.2 Confidentiality

CCTU plan to follow the principles of the UK DPA regardless of the countries where the trial is being conducted.

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Participant's data will be collected and kept securely. Confidentiality of participant's personal data is ensured by not collecting participant names and other personally identifiable information on CRFs and receiving only pseudonymised data. At trial enrolment, participants will be allocated a Participant Identification Number (PIN), which will be used on all trial related paperwork sent to UCL CCTU and in the trial database. Any documents (e.g. screening and enrolment logs) linking PIN to participant's personally identifiable information will be kept securely at the trial location; only redacted copies will be sent to Sponsor if requested.

Copies of participant's trial data will be kept at the participating trial location in a secure location with restricted access. Unless working at a trial location, CCTU staff will only have access to the data collected on the trial CRFs (i.e., they will not have access to any other personal data) and applicable source data, moreover only staff working on the trial will have access to these data. Where paper copies of CRFs have been sent to CCTU (due to central database unavailability, e.g., system updates, system failure), all CCTU copies of CRF data on paper will be stored securely in locked filing cabinets at the UCL CCTU office. Data stored electronically are held on secure servers, that have restricted access.

The informed consent form will carry the participant's name and an appropriate signature; these will be retained at the trial location (participant's hospital). The consent forms will only be accessed by UCL CCTU staff for purposes of monitoring the consent procedure at the trial location.

Trial-specific samples will be labelled with the Sample Type, Trial specific Participant Identification Number (PIN), Partial DOB (MMM, YYY), Date and Time of Collection and Visit number.

7.4 Source Data

The investigator/institution should maintain adequate and accurate source records and trial records that include all pertinent observations on each of the trial participants at the trial location. Source data are contained in source records and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source records are the first place where the source data are recorded. These can include hospital records, clinical and office charts, laboratory notes, X-rays, and pharmacy dispensing records.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source.

For this trial, the eCRFs will not be the source records for any data elements unless otherwise agreed with the STRATIFY lupus Team.

A Source Data Agreement will be put in place as part of the trial location activation process with each trial location. This will define the source records and the data therein, together with

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location of these source records and any applicable plans for transmission of source data between the trial location and CCTU.

The following data should all be verifiable from source records which may include paper notes and electronic health records:

- signed consent forms.
- dates of visits including dates any trial specimens were taken and processed in the laboratory.
- eligibility and baseline values.
- adverse events of any grade.
- serious adverse events.
- dates IMP was dispensed and (if necessary) IMP returned.
- pharmacy or clinic IMP accountability and prescription logs.
- concomitant medications.
- medical history.
- local blood results.
- pregnancy test results.
- vital signs including weight.
- physical examination.
- LupusQoL questionnaire.
- SLICC index.
- SLEDAI 2000.
- BILAG 2004.

7.5 Data Collection and Transfer Methods

Data collected will need to be directly entered by the research team at the local hospital onto the Sponsor's central database (eCRFs). Training on data collection, secure data transfer and storage for the trial location staff listed on the delegation of responsibilities log will be provided at the trial location initiation meeting or prior to green light trial location activation.

7.6 Data Management

Data will be collected at the time-points indicated in the Participant Timeline (section 5.2). The central database OpenClinica will generate the PIN e.g. in the format TSR-TN-NNN (where **TSR** = Trial Specific Reference, **TN** = Trial Location Number and **NNN** = Participant Number). Data will be entered under each participants assigned PIN onto the central database. The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on data, allowing users to raise data query requests, and search facilities to identify validation failure and missing data.

Data collection, data entry, queries raised by a member of the STRATIFY lupus trial team and database lock(s) will be conducted in line with the CCTU SOPs and trial-specific Data Management Plan.

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The database will be password protected and only accessible to members of the STRATIFY lupus trial team at CCTU, delegated staff at the trial locations and external regulators if requested. Database users will only be granted permissions to use the database functionality appropriate to their role in the clinical trial.

Identification logs, screening logs and enrolment logs will be completed and held at the trial location.

All data will be handled in accordance with the Data Protection Act 2018, the EU General Data Protection Regulation (GDPR) 2016 (and subsequent updates and modifications).

7.7 Data Storage

Trial data will be stored in a database created specifically for STRATIFY lupus trial.

The database is hosted by OpenClinica. The data are stored on secure, GDPR-compliant, cloud-based servers held within UK and EU: https://www.openclinica.com/privacy-policy/

The randomisation service is hosted by Sealed Envelope LTD. The data are stored on a secure, GDPR-compliant, cloud-based servers held within the EU: https://www.sealedenvelope.com/security/

The identification, screening and enrolment logs, linking personally identifiable information to the PIN, will be held locally by the trial location. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the trial location for 25 years after trial closure unless otherwise advised by CCTU.

7.8 Data Archiving

Once all primary and secondary analysis has been completed the trial data will be archived. Once the trial data has been archived the trial database will be decommissioned and will no longer be available. Any subsequent/ further analysis will be performed using the archived data.

7.9 Quality Issues

Quality Issues are issues that can have an impact on participant safety, rights, and well-being; data integrity and/or scientific rigor; and compliance with regulatory requirements; these can be classified as protocol deviations, potential serious breaches, near misses etc.

A protocol deviation is any departure from procedures documented in this protocol; this includes deviations that cannot be predicted. If a protocol deviation is identified the Trials team should be contacted and CCTU's protocol deviation reporting process will be followed.

A 'serious breach' is a deviation from procedures documented in this protocol, GCP or other clinical trial regulations that is likely to affect to a significant degree:

1. The safety or physical or mental integrity of the participants in the trial, or
2. The scientific value of the trial.

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If a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee and/or Regulatory authority (MHRA) within 7 days.

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8 Statistical Considerations

8.1 Sample Size

Based on the BEAT-lupus data for biomarker positive patients (IgA2 anti-dsDNA antibody levels ≥12.5AU) (difference between the two arms: 58 percentage points), for the STRATIFY lupus trial, 52 evaluable participants are needed to detect a more modest 42 percentage points difference in MCR between arms with 90% power, assuming 9% achieving an MCR in control participants. The sample size was calculated at the 5% significance level in a two-sided test of superiority of the active dose over placebo, using Fisher's exact method in STATA 18. To account for methodological challenges, including loss-to-follow-up, we adjusted the calculation by 20% and aim to recruit 66 participants into the trial.

A supportive analysis of the component parts of the composite major clinical response score using a latent variable framework[16] will also be performed. This maintains the same definition of the endpoint but can achieve an increase in precision equivalent to increasing the sample size by at least 35% in lupus trials.

8.2 Assignment of Intervention

8.2.1 Randomisation Procedures

An independent online randomisation service provider (www.sealedenvelope.com) will be used to minimise allocation bias within the trial. At the Randomisation visit, the site PI (or delegate) will enter the participant's partial DOB, date of consent and variables required for minimisation (BILAG category and ethnicity), re-confirm participant's eligibility on the SealedEnvelope.com secure online system and allocate the unique Infusion code to the participant.

Delegated staff at participating trial locations will be provided with a secure login to Sealed Envelope according to their role in the trial. The randomisation result will be shown directly online as a unique Infusion code with an email confirmation sent to the user and to the CCTU trial team. The investigator will provide details of the allocated infusion code assigned to the participant on the prescription.

Randomisation will be considered completed after a participant has had their infusion on Day 0 (Randomisation).

8.2.2 Randomisation Method

A 1:1 randomisation process using minimisation will be employed to allocate participants to either belimumab or matching placebo.

- The minimisation algorithm will incorporate a random element to ensure balance between the randomised groups by the following minimisation factors:
    - BILAG category at screening
    - Ethnicity

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8.2.3 Sequence generation

A sequence of unique infusion codes for every belimumab/placebo infusion kit will be generated by Sealed Envelope and will be entered into their web-based randomisation system. A copy of the sequence will be held securely at UCL CCTU.

Each infusion code will indicate whether the participant will receive belimumab or placebo infusions. The unblinded statistician will send the list of the infusion codes to the trial pharmacist or a delegate at each of the trial locations. When a participant is randomised by Sealed Envelope, an infusion code will be assigned for each participant's Participant Identification Number using minimisation. The pharmacist or a delegate at the trial location will dispense the trial treatment for each participant in accordance with their infusion code. The trial team will record the infusion code assigned to each participant on the CRF.

The unblinded pharmacy monitor at the CCTU along with the trial location pharmacies will ensure that appropriate amounts of belimumab/placebo kits will be delivered to trial location pharmacies to allow adequate supplies for pharmacy dispensing.

8.2.4 Allocation concealment mechanism

The list of unique STRATIFY- lupus infusion codes will be generated by Sealed Envelope. The allocation will be concealed from the participant, local investigators, and the trial team prior to assignment and during the trial to prevent allocation bias. This is supplemented by the use of the minimisation algorithm.

8.2.5 Allocation Implementation

After the participant has provided written informed consent and their eligibility for the trial has been confirmed, randomisation will be performed by the PI (or delegated member of the clinical investigating team at local trial locations) using the Sealed Envelope randomisation service stated above. Eligibility and consent will be verified before each participant is randomised. The responsibility for enrolling participants and prescribing trial medication to participants lies with the PI at each recruiting trial location. Eligibility decisions will be made in line with the approved protocol. Other delegated clinicians employed at the same clinical trial location as the PI may partake in participant enrolment and prescribe trial medication provided appropriate training has been undertaken and approval is given by the trial location PI. Individuals delegated key tasks/roles must appear on the STRATIFY-Lupus Trial Delegation log, signed off by the PI.

Trial staff at trial locations will be given a separate delegation log to request user accounts for appropriate access to the Sealed Envelope system (randomise only, randomise and unblind etc.). Individuals at participating trial locations will be provided with a secure login to the Sealed Envelope website according to the delegation of responsibilities log. The users will be required to log into the website and answer eligibility questions before entering data required for randomisation and being permitted to randomise a participant. The randomisation result will be shown directly online with an infusion code and an email confirmation sent to the user and to the UCL CCTU trial team.

The PI or delegated investigator at trial location will provide details of the allocated infusion code assigned to the participant on prescription and order forms which will be screened and

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matched to the Infusion code list by the local trial location pharmacist before the trial medication is dispensed. A full accountability trail will be maintained from receipt of trial medication by the local trial location pharmacies, prescribing of the trial medication by the local principal investigators, dispensing of the trial medication by the local trial location pharmacies to the point of destruction of undispensed/returned trial medication.

8.2.6 Blinding

STRATIFY Lupus is a double-blind trial. Only the local pharmacist at the trial locations, the sponsor and the designated sponsor unblinded statistician will be unblinded to the treatment allocation. All other members of the trial team will be blinded. Belimumab will be supplied to each pharmacy. The infusions will be made up by the trial pharmacist or delegated members of the pharmacy team in each hospital and labelled with participants' Participant Identification Number. Once prepared, belimumab and Normal Saline infusions will be indistinguishable in appearance to maintain blinding.

The use of trial infusion code ensures that the unblinding of one participant will not unblind the entire trial arm. The blinded treatment identity will be maintained in the online Sealed Envelope randomisation service except in the case of medical emergency (see 4.6.1 Emergency unblinding).

Detailed information regarding allocation implementation and blinding is provided in the STRATIFY lupus IMP Management Plan and STRATIFY lupus Randomisation and Unblinding Plan.

Participants who withdraw from the trial after randomisation is completed, will not be replaced and the treatment assignment of withdrawn participants will not routinely be revealed to the treating physician. Clinicians will be advised to devise a therapeutic plan on the assumption that the participant has received belimumab.

8.3 Statistical Considerations

8.3.1 Estimand Framework

Characteristic of Estimand	Definition
Population	Participants who have Systemic Lupus Erythematosus with active lupus, who are due to receive B cell depletion therapy as part of standard of care (SOC) and with positive serum IgA2 anti-dsDNA antibodies (≥12.5AU) at time of screening.
Treatment conditions	Belimumab 10 mg/kg versus placebo, following 4-8 weeks of Rituximab infusion.
Endpoint	Modified Major Clinical Response (MCR) at 52 weeks.
Summary measure	Exact risk difference

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Strategies for handling Intercurrent Events	
1. Death before Week 52	While alive.
2. Participant withdrawal from randomised medication	Treatment policy.
3. Participant having dose modification or dose interruption	Treatment policy.
4. Participant not complying to randomised medication as per protocol	Treatment policy.
5. Participant concomitant care not in line with protocol	Treatment policy.

8.3.2 Statistical Analysis Plan

All analyses will be performed according to an a-priori statistical analysis plan (SAP). A detailed statistical analysis plan (SAP) will be produced and reviewed by the Trial Steering Committee prior to the first substantive analysis.

A CONSORT diagram will be used to describe the course of participants through the trial. Baseline characteristics will be summarised for all randomised participants. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. The impact of missing data and non-compliance to the protocol will be investigated.

Baseline characteristics will include the percentage of participants within each of the categories defined by the minimisation factors described in **8.2.2 Randomisation Method**.

The SAP will be stored electronically in the Statistical Master File.

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8.3.3 Interim Analyses

There will be no formal interim analyses of the data however, the Independent Data Monitoring Committee (IDMC) will review the trial and safety data (at least annually) throughout the duration of the trial. The IDMC will have unrestricted access to the ongoing data collection in the trial to ensure that participants are not placed at unreasonable risk, however any analyses undertaken for those purposes will remain strictly confidential during the trial and mirror those outlined in the SAP.

No interim efficacy analyses are planned as part of the SAP; therefore, no type I error correction will be required for the primary analysis.

8.3.4 Statistical Methods – Outcomes

The primary outcome is modified major clinical response (MCR) at 52 weeks. The exact risk difference between the treatment arms will be presented with a 95% confidence interval. The p-value will be estimated from the Fisher's mid exact test.

Binary secondary outcomes will be compared between arms using exact risk difference. Time- to-event outcomes will be displayed using Kaplan–Meier curves and the stratified log rank test will be carried out. A Cox relative risk regression analysis, with adjustment for minimisation factors, will also be undertaken with the suitableness of proportional hazard assumptions examined. We will use mixed effects regression model for analysing continuous outcomes. The model will include fixed effects for intervention group (belimumab or placebo), time as categorical variable and a treatment and time interaction. A random patient effect will be included to take account for clustering. The model will be fitted using restricted maximum likelihood estimation (REML) and will be modelled with an identity covariance structure.

8.3.5 Additional Analyses - Subgroup

A logistic regression model for the primary efficacy outcome will be carried out using interaction terms to investigate the effect of treatment on pre-specified subgroups defined by the minimisation factors, BILAG category and ethnicity, if a sufficient number of MCR events are observed in the two arms.

8.3.6 Additional Analyses

No further adjusted models are planned.

8.3.7 Additional Analyses – Sensitivity

A causal mediation analysis of the effect of prednisolone on the major clinical response will be considered using the STATA mediation package.

We will consider using pattern mixture models to carry out supportive analysis if a high proportion (>10%) of participants is observed to have missing primary outcome data. Sensitivity analyses will be conducted to examine the potential influence of missing data under different pattern assumptions.

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As a supportive analysis of the primary endpoint, we will apply the augmented binary method to estimate the difference in modified MCR proportion between treatment groups. This method utilises a joint model of the different components that define modified MCR using the latent variable framework to substantially improve the efficiency, whilst retaining the same endpoint. This method can achieve an increase in precision equivalent to increasing the sample size by at least 35% in lupus trials[13]. The method showed great efficiency gains compared to analysing as a binary endpoint when applied to other SLE endpoints.

8.3.8 Analysis Population and Missing Data

The primary efficacy analysis will be conducted following the intention to treat (ITT) principle where all randomised participants are analysed in accordance with their randomised intervention.

Participants that discontinue trial medication will continue to be followed up in accordance with the trial protocol and their data included in the ITT analyses. All efforts will be made to ensure that the primary outcome data are collected for all participants. We will consider using causal mediation analysis if >20% of participants discontinue treatment early, to assess if any potential differences in treatment adherence by arm may mediate the effect of treatment on the primary outcome.

All randomised participants will be included in the safety analysis population.

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9 Economic Evaluations

No Health Economic Evaluations are planned for this trial.

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10 Regulatory & Ethical Issues

10.1 Compliance

10.1.1 Regulatory Compliance

This trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2024, as amended.

In conducting the trial, the Sponsor, UCL CCTU and the trial locations shall comply with the protocol and with all relevant guidance, laws and statutes, as amended, applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority.
- Good Clinical Practice ICH E6 (R3).
- Data Protection Act 2018 (DPA number: Z6364106).
- General Data Protection Regulation (EU)2016/679 (GDPR).
- Medicines for Human Use (Clinical Trials) Regulations 2024 (IMP trials only).

10.1.2 Trial location Compliance

Agreements that include detailed roles and responsibilities will be in place between participating trial locations and CCTU.

Participating trial locations will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary (see section 7.9).

10.1.3 Data Collection & Retention

Clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 25 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

10.2 Ethical Approvals

10.2.1 Ethical Considerations

The following ethical considerations relating to this trial have been considered extensively and every effort has been made to minimise them and their impact on participants:

- Any additional visits required by the trial.
- Any additional tests required by the trial, for example: blood.
- Use of placebo and when and/or whether its use would be revealed.
- Any washout period, its length and what the implications might be.

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- Any treatment that may be denied to the participant or withheld during the trial and the use of rescue medication.
- Any additional short-term or long-term risks of participating in the trial.
- Effects on life insurance (sometimes known as assurance) policies.
- Participants will not be able to choose their own treatment if this is a randomised controlled trial (RCT).
- Any teratogenic effects from the treatment.
- Reimbursement of time and expenses and how these rates were decided on (if payment is even available).
- The collection of sensitive or personal samples or data.
- Publication of data and feedback of overall results (not individual results) to participants.
- Blood and tissue samples as donations – not sharing in the profit in the unlikely instance that something is developed.

10.2.2 Ethics Committee Approval

Within the UK, following main REC approval and Health Research Authority (in England) approvals and before initiation of the trial at each trial location, the local information pack will be submitted to each trial location Research and Development (R&D) offices by UCL CCTU. The local information pack will contain the protocol, all informed consent forms, and information materials to be given to the prospective participant, the mNCA, the Organisation Information Document (OID), and the validated Schedule of Events Cost Attribution Template (SoECAT). In England, the R&D office will be asked to confirm capacity and capability. Any further substantial modifications will be submitted and approved by the main REC and HRA.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so, however, must be recorded; the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing their further treatment.

10.3 Competent Authority Approvals

This protocol will be reviewed by/submitted to the national competent authority (MHRA) in the UK.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by The Medicines for Human Use (Clinical Trials) Regulations 2024. Therefore, a Clinical Trial Authorisation (CTA) is required in the UK.

The progress of the trial and safety issues will be reported to the competent authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices in a timely manner.

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Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

10.4 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each trial location or to other local departments for approval as required in each country. A copy of the local permissions (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the CCTU before participants are entered.

10.5 Trial Closure

Trial closure is defined as the date when all data have been received, cleaned and all data queries resolved at all trial locations and the database locked for final analysis.

The MHRA and the REC/HRA will be notified within 90 days of trial completion. Within one year of the end of the trial, the CCTU will submit a final trial report with the results of the trial, including any publications/abstracts of the trial, to the HRA and the MHRA. In case the trial is ended prematurely, the CCTU will notify the HRA and the MHRA within 15 days, including the reasons for the premature termination.

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11 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

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12 Finance

STRATIFY lupus is fully funded by Arthritis UK and the Department of Health and NIHR Reference: 23233. It is not expected that any further external funding will be sought.

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13 Oversight & Trial Committees

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary.

There are several committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

13.1 Trial Management Group

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and CCTU staff. The TMG will be responsible for the design, coordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG Terms of Reference.

13.2 Trial Steering Committee

The Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. The membership, frequency of meetings, activity and authority will be covered in the TSC Terms of Reference.

13.3 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to the confidential, accumulating data for the trial. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data, and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity and authority will be covered in the IDMC Terms of Reference. The IDMC will advise the TSC through its Chair.

13.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

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14 Patient & Public Involvement

Patient and Public Involvement (PPI) in research is defined by INVOLVE (an advisory group established by the NIHR) as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. INVOLVE intends 'public' to include patients, potential patients, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In some cases, this may include involvement of a trial's participants in guidance or oversight of a trial.

14.1 Potential Impact of PPI

Interested patients and public have been invited to be involved in the study design and recruitment strategy for this study.

Input from the PPI group ensures that this is a relevant area of research for them. They have been consulted on study design to ensure their needs and preferences are considered which will ensure a patient-centred study.

The group have been consulted on recruitment strategies to increase recruitment and retention, especially for groups that are traditionally underrepresented in clinical research.

14.2 Identifying PPI Contributors

Past participants of the BEAT Lupus study, members of the UCLH Rheumatology Research Patient and Public Involvement Group and patients from UCLH clinics have been invited to form a PPI committee for this study.

Care has been taken to invite members of diverse backgrounds and demographics to ensure the unique perspectives of diverse communities are embedded in the research design and recruitment strategy.

The University College London Hospital Patient and Public Involvement (UCLH PPI) Rheumatology Research group is a well-established group which has been operating for over four years. Introduction materials are shared with new members in the form of a Terms of Reference document. There will be a quorum of four patient participants in the PPI consultation group, should attendance fall below this number, others will be invited.

Participants of the group are reimbursed for their time, expertise, and any acquired expenditure (travel/childcare) based on the INVOLVE tariff.

14.3 Protocol Design & Trial Set Up

Prior to seeking funding for this trial, a PPI meeting was held to discuss participation in the previous trial, BEAT Lupus[25], and elements of this future trial. Participants commented on visit schedules, sample collection, and IMP administration. Preferences have been embedded in STRATIFY Lupus study design. Budget for PPI activities and participants reimbursement has been included in the trial costings.

14.4 PPI in the Ongoing Running of the Trial

Further PPI meetings will be held on a virtual platform (Zoom or Teams) at the following time points:

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a. once funding for the study has been confirmed, before submission to ethic committees to ensure study design is satisfactory and participant facing documents and communications have been reviewed.
b. Prior to commencement of recruitment to further discuss recruitment strategies.
c. After one year of recruitment to share how recruitment is progressing, discuss retention of participants and any issues with study design and adverse events.
d. At end of study to discuss thoughts about participation in the study.
e. At publication of results to share trial outcomes.

Ad hoc meetings may be called for time sensitive discussion of any issues that may arise.

Reimbursement for time spent in meetings and preparation time and time spent reviewing documents will be offered at INVOLVE tariff rates.

14.5 Interpreting & Evaluation Impact of PPI

The Public Involvement in Research Impact Toolkit will be used to assess the impact of patient and public involvement in this study.

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15 Publication & Dissemination of Results

15.1 Publication Policy

15.1.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. The publication of the results will comply with the UCL CCTU Publication Policies.

A lay summary of the results will also be produced to be disseminated to those participants who took part. and will be communicated by at least one of the following methods:

- End of trial information sheet or newsletter provided by CCTU to each trial location.
- Sponsor trial website.
- Verbal information provided by the trial locations.

A summary of results will be submitted to the REC via the HRA (https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/final-report-form/) and published through an open-access mechanism in a peer-reviewed journal within 12 months of the trial closure.

A summary of results will be published within 12 months of the end of study, in the registry where the clinical trial is registered and/or by a third party or third parties.

15.1.2 Authorship

All individuals who have made substantial intellectual, scientific and practical contributions to the trial and the manuscript should, where possible, be credited as authors; all individuals credited as authors should deserve that designation. It is the responsibility of the Chief Investigator and, ultimately, the Sponsor to ensure that these principles are upheld.

15.1.3 Reproducible Research

The most recent version of the protocol will be made available as supplementary material upon publication of the final clinical investigation report.

Applications for access to the trial dataset at the end of the trial, should be submitted formally in writing to UCL CCTU and will be considered, and approved in writing after formal consideration by the trial oversight committees and the CI.

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16 Data and/or Sample Sharing

Data will be shared according based on the following principles:

- No data should be released that would compromise an ongoing trial or study.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Data will be available for sharing within 12 months of the end date. Researchers wishing to access STRATIFY lupus data should contact the Trial Management Group in the first instance.

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17 Protocol Modifications

Table 13. Summary of Protocol modifications

Protocol version	Protocol date	Summary of changes
V1.0	13th January 2026	N/A – new document
V2.0	14th May 2026	**Structured trial summary and section 3.2 participant exclusion criteria:** Exclusion criterion #18 revised to apply an IgA exclusion threshold of <10mg/dL, in alignment with the SmPC as per MHRA/REC feedback. **Sections 3.2.1 and 3.2.2:** Superscript numbers 17 and 18 updated to 15 and 16 in line with section 18 (reference list) and references added as per MHRA/REC feedback. **Section 18:** Updated reference 15 to 17 in line with the change in section 3.2.1 and section 3.2.2.
V3.0	9th September 2026	**Structured Trial Summary:** CTA #, REC #, ISRCTN ID, Date of registration in Primary Registry have been added. Exclusion criteria 3 “36 months” updated “6 months”. Date of first enrolment has been updated. **Roles and responsibilities:** Role of Kashfia Chowdhury and Eleanor Hawkin’s affiliation has been updated. **Trial Diagram:** Updated to add RNA samples. **Section 3.2:** Exclusion criteria 2 wording updated to match wording in Structured Trial Summary. Exclusion criteria 3 “3 months” updated to “6 months”. **Section 3.7:** Title of section updated. Section updated to detail mandatory and optional samples information. **Section 4.4:** Wording change in reference to glucocorticoids use. **Participant Timeline (5.2):** Addition of visit number “0” to first screening visit. “Urine” added to dipstick. Added the acronym PGA in expanded form to Participant Timeline. Footnotes updated to add clarity on use of total IgG versus IgG anti-dsDNA. PCR Footnote updated to add "urine" and "urine dipstick" changed to "protein dipstick".

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		RNA, PBMC and stool sample collection removed from week 12 timepoint. "ACR" added to PCR; dispense of trial treatment and administration of trial treatment combined; total IgG, IgA and IgM added. **Section 18:** Reference 5 removed. Reference list and superscript throughout the protocol updated. Reference to patient updated to participant updated throughout the protocol. IgA2 anti-DNA updated to IgA2 anti-dsDNA throughout the protocol. Shipping of screening serum IgA2 anti-dsDNA antibody samples updated from one working day to day of collection throughout the protocol. Grammatical and typographical errors updated throughout the protocol.

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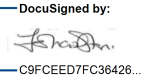
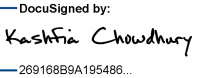
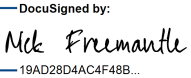
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