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A Phase 3, multicentre, randomised, double-blind, placebo-controlled, 104-week study of subcutaneous belimumab administered in combination with rituximab in adults with systemic lupus erythematosus (SLE): BLISS-BELIEVE study protocol

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ABSTRACT

Introduction: Belimumab, an anti-B-lymphocyte-stimulator antibody, is approved for the treatment of active, autoantibody-positive systemic lupus erythematosus (SLE). Rituximab, a B-cell-depleting anti-CD20 antibody, remains in the SLE treatment armamentarium despite failed trials in lupus nephritis and extra-renal lupus. These biologics, which operate through complementary mechanisms, might result in an enhanced depletion of circulating and tissue-resident autoreactive B lymphocytes when administered together. Thus, belimumab and rituximab combination may be a highly effective treatment of SLE. This study aims to evaluate and compare the efficacy, safety and tolerability of subcutaneous (SC) belimumab and a single cycle of rituximab in patients with SLE with belimumab alone.

Methods and analysis: BLISS-BELIEVE is a 3-arm, randomised, double-blind, placebo-controlled, 104-week superiority study. Two hundred adults with SLE will be randomised 1:2:1 to Arm A, belimumab SC 200 mg/week for 52 weeks plus placebo at Weeks 4 and 6; Arm B, belimumab SC 200 mg/week for 52 weeks plus rituximab 1000 mg at Weeks 4 and 6; Arm C, belimumab SC 200 mg/week plus standard therapy for 104 weeks. The 52-week treatment period (Arms A and B) is followed by a 52-week observational phase. The primary efficacy endpoint is the proportion of patients with disease control (SLE Disease Activity Index (SLEDAI)-2K ≤2, without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day) at Week 52. Major secondary efficacy endpoints are the proportion of patients in clinical remission (defined as SLEDAI-2K =0, without immunosuppressants and corticosteroids) at Week 64, and the proportion of patients with disease control at Week 104. Safety endpoints include the incidence of adverse events (AEs), serious AEs and AEs of special interest.

Ethics and dissemination: Within 6 months of the study's primary manuscript publication anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Trial registration number: NCT03312907

ARTICLE SUMMARY

- This study builds on the experience of randomised controlled trials of the biologics belimumab and rituximab used as single agents, as well as pre-clinical findings, case studies and open-label trials of belimumab and rituximab combination treatment

- The unique sequence of treatment administration, and assessment of the clinically relevant outcomes of disease control and disease remission, are novel features of this study

- BLISS-BELIEVE is the first randomised trial to carry out observations for 52 weeks after stopping belimumab treatment, allowing for the assessment of true disease remission and its durability

- BLISS-BELIEVE randomises patients to a third treatment arm of belimumab plus standard-of-care therapy, to reflect current real-life practice

- The study is limited by a relatively small sample size, and thus has limited power to detect infrequent adverse events

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) share some common molecular pathways that lead to inflammation, which results from dysregulation of the normal immune response. Chronic inflammation in IMIDs is associated with progressive tissue damage as well as increased co-morbidity and mortality. Systemic lupus erythematosus (SLE) and Sjögren's syndrome are both prototypic antibody-dependent IMIDs.[1] SLE is a chronic multisystem inflammatory autoimmune disease associated with impaired health-related quality of life.[2 3] The ultimate goals of SLE treatment are disease remission, damage prevention (from both disease progression and prolonged use of medication) and normalisation of health-related quality of life.[4 5] These goals are difficult to achieve in most patients owing to limitations in the efficacy of, and long-term toxicity associated with, conventional treatments for SLE, such as corticosteroids and immunosuppressants.[6 7]

Patients with SLE have elevated levels of circulating B-lymphocyte stimulator (BLyS), a member of the tumour necrosis factor ligand superfamily that promotes B cell activation and differentiation.[8-10] Increased serum BLyS levels in patients with SLE are associated with disease activity, disease relapse and increased numbers of autoantibody-secreting plasma cells, linking BLyS to the pathogenesis of SLE.[9 11] Belimumab, a recombinant immunoglobulin G1λ human monoclonal antibody, binds to and antagonises the biological activity of soluble BLyS.[12] It has shown efficacy in patients with autoantibody-positive active SLE in multiple trials.[13-16] Belimumab-treated patients also experienced fewer disease flares, and showed a reduction in steroid use and long-term organ damage accrual compared with patients receiving standard of care (SoC).[13-17] While the efficacy of belimumab has been demonstrated in patients with SLE, a proportion of patients maintain a degree of disease activity despite belimumab treatment.[13-16] Therefore, additional effective and well-tolerated treatment options are required to further improve overall disease control.

Rituximab is a B-cell-depleting, anti-CD20 monoclonal antibody that showed promise in several open-label clinical studies,[18-22] but failed to demonstrate efficacy in two randomised trials in SLE and lupus nephritis.[23 24] In autoimmune diseases, rituximab treatment results in rapid and near complete depletion of circulating CD20+ B cells; however, relatively high numbers of B cells persist in tissues, such as bone marrow, kidneys, synovium and salivary glands.[25-29] In SLE, an increase in BLyS levels after rituximab treatment may contribute to survival and rebound of autoreactive B cells and subsequent disease

flares,[30 31] as demonstrated in several cohort studies.[32-34] Consistent with these observations, reduced maturation of autoreactive B cells during B-cell reconstitution was observed in mice treated with an agent that blocked B-cell activating factor.[35]

Combining belimumab with rituximab therefore has a strong immunological rationale, as the drugs operate through complementary and perhaps synergistic mechanisms.[36] Belimumab treatment results in the mobilisation of memory B cells from tissues despite an overall decrease in peripheral B cell levels.[37] This phenomenon will render tissue-resident B cells more susceptible to depletion by rituximab. In addition, blocking the effects of high serum BLyS levels might have favourable quantitative and qualitative effects on B-cell reconstitution after depletion.[31] Synergistic or additive effects of such a combination have indeed been demonstrated in pre-clinical studies in lupus-prone mice. Improved tissue B-cell subset depletion, a decrease in the levels of autoantibodies, reduced proteinuria and improved survival were observed with combination therapy compared with either treatment alone.[38-40]

This hypothesis is further supported by case reports in patients with SLE, lupus nephritis and Sjögren's syndrome,[41-45] and prompted the SynBioSe study, which showed significant clinical and immunological improvements from baseline in patients with refractory SLE who received rituximab and belimumab.[46] Several clinical trials are currently investigating belimumab and rituximab combination therapy in primary Sjögren's syndrome (NCT02631538), lupus nephritis (CALIBRATE; NCT02260934), and SLE (BEAT Lupus; ISRCTN47873003).

We hypothesised that durable low disease activity might be achieved in patients with active SLE by re-setting the autoreactive humoral immune system. Therefore, we have designed the BLISS-BELIEVE study to examine whether combination treatment with belimumab and rituximab could induce a pre-defined state of disease control or disease remission, allowing the tapering of conventional SLE therapies. This study will employ a novel sequence of belimumab and rituximab combination therapy and investigate novel study endpoints, which could potentially shift the current paradigm of SLE treatment.

The objective of this study is to evaluate the efficacy, safety and tolerability of subcutaneous (SC) belimumab and a single cycle of rituximab administered in a combination regimen in adult patients with SLE compared with belimumab alone.

METHODS AND ANALYSIS

Study design

This is a Phase 3, multicentre, 3-arm, randomised, double-blind, placebo-controlled, 104-week superiority study (205646; NCT03312907). There will be a 52-week double-blind treatment period followed by a 52-week double-blind observational treatment-free follow-up period in Arms A and B (to Week 104) (**Figure 1**). The study began recruitment in March 2018, with an estimated final completion in June 2021.

Study population

Detailed inclusion and exclusion criteria are listed in **Table 1**. Briefly, patients must be ≥18 years of age, with a clinical diagnosis of SLE according to the American College of Rheumatology criteria, and a SLE Disease Activity Index (SLEDAI)-2K score ≥6 at screening. Patients with severe lupus nephritis or severe active central nervous system lupus will be excluded. Informed consent will be obtained from patients prior to the initiation of any study procedures or study-specific data collection.

Table 1: Patient inclusion and exclusion criteria

Inclusion criteria
≥18 years of age
Clinical diagnosis of SLE according to the ACR criteria
Minimum screening SLEDAI-2K score ≥6
Unequivocally positive ANA and/or anti-dsDNA test results from two independent time points
Stable SLE treatment regimen
Female patients not pregnant, not breastfeeding, not of childbearing potential or follow contraceptive guidance
Exclusion criteria
Symptomatic herpes zoster within 3 months prior to screening
Active or latent TB, confirmed by medical history and examination, chest X-rays, and TB testing: either a positive TST (defined as a skin induration ≥5 mm at 48–72 hours, regardless of BCG or other vaccination history), or a positive QuantiFERON-TB Gold test
Allergies to humanised monoclonal antibodies
Clinically significant multiple or severe drug allergies and/or history of hypersensitivity to belimumab and/or rituximab
Lymphoma, leukaemia, or any malignancy within the past 5 years
ALT >2x ULN
Bilirubin >1.5x ULN

IgA < 10 mg/dL
IgG < 250 mg/dL
Neutrophils < 1.5 x 10^9
Unstable liver or biliary disease
Severe heart failure
QTc >450 msec or >480 msec in patients with bundle branch block
History of a major organ transplant
Clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE
Acute or chronic infection requiring management
Severe lupus kidney disease
Severe active central nervous system lupus
Planned surgical procedure, laboratory abnormality, or condition that makes the patient unsuitable for the study
Evidence of serious suicide risk
History of an anaphylaxis reaction to parenteral administration of contrast agents, human/murine proteins, or monoclonal antibodies
Live vaccine(s) within 1 month prior to screening
Within 364 days of Day 1, received certain biologics (belimumab, rituximab, abatacept, a B-cell-targeted therapy, a biologic investigational agent other than B-cell-targeted therapy), or required 3 or more courses of systemic corticosteroids
Within 90 days of Day 1, received anti-TNF therapy, interleukin-1 receptor antagonist, intravenous immunoglobulin, high-dose prednisone or equivalent, or plasmapheresis
Within 60 days of Day 1, received a non-biologic investigational agent, intravenous cyclophosphamide, a steroid injection
Positive HIV antibody test
Positive serology for hepatitis B or hepatitis C
Current or history (within 364 days of Day 1) of drug/alcohol dependence
Sensitivity to any of the study treatments or components
Unable to administer belimumab by SC injection

ACR, American College of Rheumatology; ALT, alanine aminotransferase; ANA, anti-nuclear antibodies; BCG, Bacillus Calmette-Guerin; IgA, immunoglobulin A; HIV, human immunodeficiency virus; IgG, immunoglobulin G; SC, subcutaneous; QTc, corrected QT; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index; TB, tuberculosis; TNF, tumour necrosis factor; TST, tuberculin skin test; ULN, upper limit of normal

Randomisation

Patients will be randomised 1:2:1 to one of three treatment arms: belimumab plus placebo (Arm A, control), belimumab plus rituximab (Arm B, combination), or belimumab plus SoC (Arm C, reference). At randomisation, patients will be stratified by their screening SLEDAI-2K score (≤9 vs ≥10), immunosuppressant use (immunosuppressant use vs no use), and corticosteroid dose (prednisone equivalent ≤10 mg/day vs >10 mg/day). Randomisation, and the first dose of belimumab, should be completed within 35 days of the initiation of screening.

Blinding

The study is double-blind with regards to whether participants are randomised to Arm A or Arm B. Randomisation to Arm C will not be blinded. To minimise bias given that Arm C is open-label, independent assessors blinded to treatment group will conduct the SLEDAI-2K assessments at selected visits for the primary and major secondary efficacy endpoints. Unblinded safety data will be reviewed regularly by an Independent Data Monitoring Committee.

Study treatments

Patients randomised to Arm A (control) will receive belimumab SC 200 mg/week for 52 weeks with a cycle of intravenous (IV) placebo (rituximab matched; dose 1 at Week 4 and dose 2 at Week 6). Patients randomised to Arm B (combination) will receive belimumab SC 200 mg/week for 52 weeks with a cycle of rituximab IV (1000 mg doses given at Week 4 and Week 6). Patients randomised to Arm C (reference) will receive belimumab SC 200 mg/week plus SoC, including immunosuppressants, for 104 weeks. Patients in Arms A and B will be administered a pre-medication regimen 30 minutes before each placebo or rituximab infusion, consisting of methylprednisolone IV 100 mg or equivalent, an oral antihistamine, and acetaminophen or equivalent (**Table 2**).

Table 2: Study treatment arms

Treatment	Arm A (control)	Arm B (combination)	Arm C (reference)
Belimumab	Belimumab SC 200 mg/week for 52 weeks	Belimumab SC 200 mg/week for 52 weeks	Belimumab SC 200 mg/week plus SoC for 104 weeks
Rituximab or matched placebo	One cycle of placebo IV (rituximab matched)	One cycle of rituximab IV 1000 mg at	None

	at Week 4 and Week 6	Week 4 and Week 6	
Pre-medication (30 minutes before each placebo or rituximab infusion)	Methylprednisolone IV 100 mg or equivalent, oral antihistamine, acetaminophen or equivalent	Methylprednisolone IV 100 mg or equivalent, oral antihistamine, acetaminophen or equivalent	None
Post Week 52 therapy	Antimalarials, NSAIDs, and/or corticosteroids with a prednisone equivalent dose of ≤5 mg/day	Antimalarials, NSAIDs, and/or corticosteroids with a prednisone equivalent dose of ≤5 mg/day	Continue belimumab SC 200 mg/week plus SoC

IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; SC, subcutaneous; SoC, standard-of-care

After completing Week 52, patients in Arms A and B will enter into the 52-week treatment-free (defined as no active treatment with belimumab and/or rituximab), observational phase of the study (Weeks 53 through 104). Patients in Arm C will continue to receive belimumab SC and stable immunosuppressants during this phase. In addition, treatment with antimalarials, non-steroidal anti-inflammatory drugs, and corticosteroids (prednisone equivalent ≤5 mg/day) is allowed in the observational phase in all three arms.

Patients considered treatment failures (patients in Arm A or B who fail to respond adequately to study treatment, who do not meet the corticosteroid taper rules or tolerate immunosuppressant withdrawal at Week 4, or who require additional therapy) will be encouraged to remain in the study to receive all safety and efficacy assessments through Week 104. During this time (Weeks 53–104), additional treatment may be given, if deemed of benefit by the investigator, to patients with responses that do not reach the predefined study criteria for disease control (as defined in the study endpoints), or subsequently experience increased disease activity. This treatment can include belimumab, corticosteroids, and/or immunosuppressants; additional treatment with rituximab will be permitted, but not encouraged.

Concomitant medications

Patients randomised to Arms A and B who enter the study on immunosuppressants will discontinue immunosuppressants at or prior to the Week 4 visit. Patients in Arm C who enter the study on stable immunosuppressants may continue to receive them throughout the study. After the initial 12 weeks of

study treatment, a protocol-specified corticosteroid taper will be initiated for all three arms. Antimalarials and non-steroidal anti-inflammatory drugs may be used throughout the study for all treatment arms.

Other investigational agents (or co-enrolment into another study of a different investigational agent), anti-tumour necrosis factor therapy, other biologics with effects on the immune system, immunoglobulin IV, cyclophosphamide IV, and plasmapheresis are prohibited throughout the study.

Study endpoints

The primary efficacy endpoint is the proportion of patients with disease control at Week 52, defined as a SLEDAI-2K score of ≤2, achieved without immunosuppressants and with a prednisone equivalent dose of ≤5 mg/day. The major secondary efficacy endpoints are the proportion of patients in clinical remission at Week 64 (defined as a clinical SLEDAI-2K score of 0, allowing for serologies of anti-dsDNA and hypocomplementemia and achieved without immunosuppressants and corticosteroids), and the proportion of patients with disease control at Week 104 (defined as a SLEDAI-2K score of ≤2, achieved without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day). Safety endpoints include the incidence of adverse events (AEs), including serious AEs (SAEs) and AEs of special interest (AESI). The endpoints will be assessed using the measures listed in **Table 3**.

Table 3: Study assessments

Efficacy assessment
SLEDAI-2K, a clinical index for measuring SLE disease activity in the previous 10 days, at screening/baseline and at Weeks 52, 64 and 104
Safety assessment
Full physical examination, electrocardiogram, clinical safety laboratory assessments, neurological assessment, and suicidal risk monitoring (assessed via C-SSRS) at screening. Symptom-driven physical examination, vital signs, clinical safety laboratory assessments, neurological assessment, and suicidal risk monitoring at scheduled and unscheduled visits
Laboratory tests
Anti-dsDNA/ANA, complement C3/C4, serum immunoglobulin (IgG, IgA, IgM), urine testing (urinalysis, spot urine protein), haematology and blood chemistry, pregnancy test: performed at screening and at each assessment visit. Autoantibody levels, including aCL, beta-2-glycoprotein, lupus anticoagulant, and extractable nuclear antigens, will be measured at Day 1 and Weeks 8, 26, 52, 60, 80, and 104
B-cell analyses

Pharmacokinetics

aCL, anti-cardiolipin; ANA, anti-nuclear antibodies; C, complement; C-SSRS, Columbia-Suicide Severity Rating Scale; Ig, immunoglobulin; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLE, systemic lupus erythematosus

Sample size calculation

Approximately 400 patients will be screened, with a goal of randomising at least 200 patients (50% screen failure rate). A target of 50 patients will be randomised in Arms A and C, and 100 patients in Arm B. This sample size provides at least 95% power (for the comparison of Arm B to Arm A at Week 52) at a 5% level of significance, assuming the underlying response in the control arm is 10%, and the true population effect is ≥25% with treatment Arm B (assumed response rate of 35%). For the primary endpoint, patients who drop out from the study will be included in the analysis as non-responders; thus, the assumed responder rates for Arms A and B already account for the rate of patient dropout. However, to ensure adequate safety exposure in Arm B, the sample size may be increased up to 300 patients if the dropout rate reaches 10% at the scheduled time point for receiving both doses of placebo or rituximab.

Based on limited clinical data with therapies including both belimumab and rituximab, opinions from external experts, and the rarity of remission or disease control seen in published studies, a rate of 35% of patients in Arm B achieving a state of disease control is considered to be highly clinically significant in SLE care. A response rate of 10% at Week 52 was assumed for Arm A (control), based on historical data from three belimumab Phase 3 trials. Assuming a 10% control responder rate and 50 patients in Arm A and 100 patients in Arm B, the minimum detectable effect at $p<0.05$ is a 12% improvement (i.e., an observed improvement of 12% or more in Arm B would give a $p<0.05$). A sample size sensitivity analysis was conducted on the primary endpoint to investigate the impact on power if the assumed underlying control response rate deviates from 10% or the treatment difference deviates from 25%.

Statistical analyses

Unless otherwise stated, all analyses will be performed on the intent-to-treat population. The key analyses will compare belimumab with or without a single cycle of rituximab (Arm A vs Arm B). Descriptive statistics will be used to compare the combination of belimumab with a single cycle of rituximab (Arm B) versus belimumab with SoC (Arm C). The primary and major secondary endpoints will

be compared using a logistic regression model. The independent variables will include treatment group, baseline SLEDAI-2K score (≤9 vs ≥10), immunosuppressant use at baseline (immunosuppressant use vs no use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs >10 mg/day). If any factor fails to converge it will be removed from the logistic model. If the model fails to converge (e.g. owing to a small number of responders), the endpoints will be analysed using a Fisher's exact test. Missing data are accounted for in the primary efficacy endpoint, as all patients will be classified as either a non-responder (including premature study discontinuation or treatment failure prior to Week 52) or responder. Sensitivity analyses will be used to explore the impact of missing data and treatment failure imputation. Descriptive statistics will be used to summarise AEs, SAEs, AESI, changes in laboratory parameters, and immunogenicity.

Ethical considerations

This study will be conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines, applicable International Conference on Harmonisation Good Clinical Practice Guidelines, and applicable laws and regulations. The protocol has been reviewed and approved by institutional review boards (IRB)/independent ethics committees (IEC). The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. SAEs will be reported by the investigator to the sponsor immediately, and no later than within 24 hours. Written informed consent will be obtained from all patients, who will be assigned a unique identifier; all patient records and data transferred to the sponsor will contain the identifier only.

Dissemination

Study information will be publicly available at www.clinicaltrials.gov, and the results of this trial (positive and negative) will be submitted for publication in relevant peer-reviewed publications and the key findings presented at national and international conferences. Within 6 months of the publication of the primary manuscript for this study, anonymised individual participant data, the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset, and clinical study report will be available for research proposals approved by an independent review committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access

agreement will be required. This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations for protocol reporting.[47]

Patient and public involvement

Patients and/or public were not involved in the development of this study.

DISCUSSION

This study aims to explore the potential for synergy and to demonstrate greater efficacy of combination treatment with belimumab and rituximab compared with belimumab monotherapy in achieving low disease activity, disease remission, or clinical quiescence in patients with SLE. Although to date, combination biologics have not been widely used in other diseases, we think there is a strong immunological rationale to study belimumab and rituximab combination therapy in the context of SLE. The residual disease activity that many patients with SLE experience despite current therapies, further justifies the exploration of this novel combination treatment. If this study confirms our hypothesis that combined belimumab and rituximab treatment has additional efficacy over standard belimumab care, then this may transform the current treatment paradigm, allowing patients with SLE to discontinue conventional, often toxic medications.

The unique sequence of administering belimumab and rituximab (which we believe will enhance B cell depletion), the use of belimumab SC and a larger sample size, differentiate the BLISS-BELIEVE study from BEAT Lupus (ISRCTN47873003),[48] a similar belimumab and rituximab combination therapy, Phase 2 trial in SLE that is currently recruiting patients in the UK. The sequence of treatment administration also differs from that used in the CALIBRATE trial in lupus nephritis (NCT02260934).[49] In addition, BLISS-BELIEVE is one of the first trials of belimumab to carry out assessments for 52 weeks after stopping treatment, and investigate ambitious, clinically relevant outcomes of low disease activity or disease remission. The 52-week observational, treatment-free phase provides an opportunity to observe if a true disease remission occurs, and allows for the assessment of the durability of any such remission or low disease activity. In the treatment of SLE, it is important to balance clinical efficacy and therapy-related toxicity. The unique design of BLISS-BELIEVE will ensure this is assessed through the use of

rigorous endpoints (such as clinical remission), and by enabling the termination of belimumab if toxicity is an issue.

The unique treatment schedules were selected according to a rationale based on the current evidence. In the 52-week treatment phase, belimumab SC 200 mg will be administered weekly as per the treatment regimen in the Phase 3 study of belimumab SC, which demonstrated its safety and efficacy in patients with SLE.[15] Rituximab is not approved for the treatment of patients with SLE, and no standard dosing regimen has been established. Based on previous trials of rituximab that showed a lack of efficacy, we deemed that a rituximab-only arm would fail to meet standards of equipoise. In the current study, rituximab dosing will follow one cycle of the approved dosing recommendation for rheumatoid arthritis, which is two doses of 1000 mg IV given 2 weeks apart. In a Phase 2/3 trial, this rituximab regimen demonstrated rapid depletion of CD19-positive cells (<5 cells/µL) in the majority of patients with SLE.[23] It is also the dosing regimen recommended in NHS England's Interim Clinical Commissioning Policy Statement for rituximab use in patients with refractory SLE.[50] Furthermore, belimumab and rituximab combination treatment has previously shown acceptable safety and significant clinical responses in patients with severe, refractory SLE.[46]

Separating the administration of belimumab and rituximab may allow for observation of safety events attributable to each treatment; however, owing to the relatively small sample size, the study will have limited power to detect less common AEs. With the consecutive administration regimen, the study allows investigation of the hypothesis that belimumab mobilises additional CD20+ B cells into the circulation, making them available for anti-CD20 treatment with rituximab. Therefore, we will be able to further establish whether more efficient depletion of autoreactive B cells, otherwise protected from cell death in the tissue niches, is achieved.[37] We anticipate that there will be fewer autoreactive B cells appearing in the memory B-cell compartment during the early phase of B-cell reconstitution. However, we are aware that the controls for this analysis are historical, owing to the ethical considerations discussed above. B-cell mobilisation will be evaluated by comparing baseline, pre-belimumab B-cell levels with autoreactive B cells appearing in peripheral blood after belimumab treatment. The possible reappearance of autoreactive B cells following rituximab treatment will then be established by comparing B cells levels between the belimumab only and belimumab and rituximab arms.

This study has some limitations. Because rituximab is not approved for the treatment of patients with SLE, a rituximab-only arm could not be included in the protocol. Therefore, clinical and serological outcomes attributable to rituximab treatment will not be assessed. However, this study aims to explore whether belimumab treatment can be optimised by sequential treatment with rituximab, for which a rituximab-only arm is not required. Another limitation of the study design is that direct measurements of B-cell depletion in tissue niches will not be performed. However, this measurement and a rituximab-only arm are being explored in a clinical trial of belimumab and rituximab combination therapy in primary Sjögren's syndrome (NCT02631538), which follows a similar administration regimen. Another limitation is that patients in Study Arms A and B will discontinue immunosuppressants, which might result in a higher than predicted dropout rate. Although substantially different from previous belimumab trials, such as BLISS 76, in which more than half the patients continued on background immunosuppressive agents,[12] this regimen will allow investigation of whether belimumab and rituximab combination therapy could result in an immunologically more favourable condition in some patients, thus enabling the tapering of conventional immunosuppressive drugs and possibly an immunosuppressant-free honeymoon. A positive outcome of BLISS-BELIEVE would further support the rationale to test this therapeutic strategy in Sjögren's syndrome and other autoantibody-dependent IMIDs.

In conclusion, the BLISS-BELIEVE study is supported by strong scientific rationale from pre-clinical studies, case reports and open-label trials. Its pioneering and unique design will allow for a long-term observation of true clinical remission, assessment of the durability of such a remission state, and assessment of any potential safety issues. The results of this study may support the rationale for combination therapy in other autoimmune conditions. BLISS-BELIEVE began recruitment in March 2018, with estimated study completion in June 2021.

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CONTRIBUTORS:

PPT initiated this study and has been involved in its design. **YKOT, INB, RAF, RFvV, DG, JG, RBH, MO,** and **PPT** were involved in the development of the study protocol, preparation of the manuscript and its subsequent revisions, and provided final approval of the version published. **BD** was involved in the preparation of the manuscript and its subsequent revisions, and provided final approval of the version published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS:

YKOT's work is funded by the Netherlands Scientific Organisation and the Dutch Kidney Foundation (KJPB12.028 & 17OKG04). **INB** is a National Institute for Health Research (NIHR) Senior Investigator and is funded by Arthritis Research UK and the NIHR Manchester Biomedical Research Centre; the views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. INB has also received speaker's bureau and advisory board grants from UCB, has participated in advisory boards and steering committees for Astra Zeneca, is a member of Independent Data Safety Boards for Medimmune and Merck Serono, has received grants from Genzyme Sanofi, and has participated in advisory boards for Eli Lilly. **BD** is an investigator on the CALIBRATE study, which is sponsored by National Institute of Allergy and Infectious Diseases. **RAF** has received grants and is a consultant for GSK and Genentech/Roche. **RFvV** has received grants and is a consultant for AbbVie, BMS, GSK, Pfizer, and UCB, and is a consultant for Celgene, Biotest, Janssen, Lilly, and Novartis. **DG** was an employee of GSK at the time of protocol development, and holds shares in BMS. **JG, RBH, MO** (and her husband), and **PPT** are employees of GSK and hold shares in the company. **RBH** has a patent pending (patent number WO 2017050833 A1) related to this work.

ETHICS APPROVAL:

The protocol has been approved by IRB/IEC. Each study site has obtained relevant IRB/IEC approvals.

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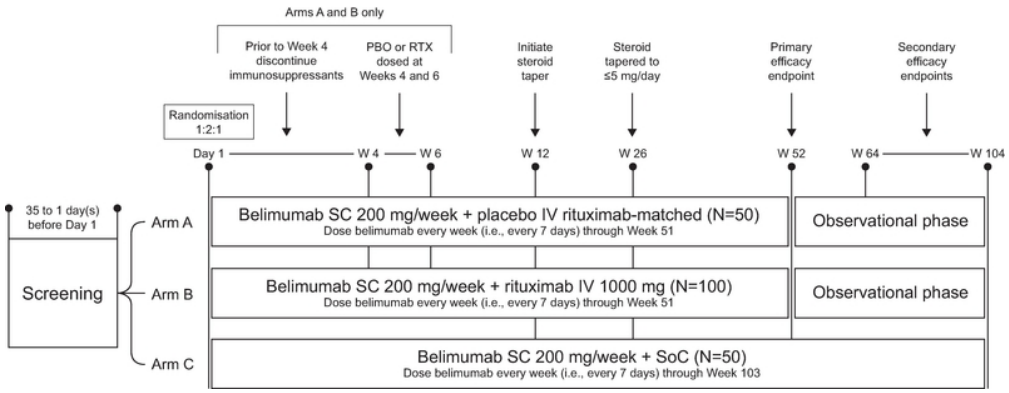
Figure 1: Study design

IV, intravenous; PBO, placebo; RTX, rituximab; SC, subcutaneous; SoC, standard-of-care; W, week



Study Design
IV, intravenous; PBO, placebo; RTX, rituximab; SC, subcutaneous; SoC, standard-of-care; W, week

67x25mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number in the manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_2 and 6_____
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (protocol p.1)
Protocol version	3	Date and version identifier	Yes (protocol p.1)
Funding	4	Sources and types of financial, material, and other support	_____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1 and 15_____
	5b	Name and contact information for the trial sponsor	Yes (protocol p.1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__15–16____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Yes (protocol p.99)

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4–5_____
	6b	Explanation for choice of comparators	___13–14____
Objectives	7	Specific objectives or hypotheses	___5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Listed in the clinicaltrials.gov record
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__6–7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___8–9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Yes (protocol p.58)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___9–10_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___10–11_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_23 (Figure 1)_
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____N/A_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Yes (protocol p.56)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Yes (protocol p.56)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Yes (protocol p.56)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Yes (protocol p.56)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Yes (protocol p.57)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Yes (protocol p.100)

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____7_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Yes (protocol p.100)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____9_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____9_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Yes (protocol p.99)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Yes (protocol p.88)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____9–10_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Yes (protocol p.88)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____9_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Yes (protocol p.98)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Yes (protocol p.98)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____9–10_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___13_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Yes (protocol p.88)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___10_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___13_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___10_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__No_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes (protocol)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

A Phase 3, multicentre, randomised, double-blind, placebo-controlled, 104-week study of subcutaneous belimumab administered in combination with rituximab in adults with systemic lupus erythematosus (SLE): BLISS-BELIEVE study protocol

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A Phase 3, multicentre, randomised, double-blind, placebo-controlled, 104-week study of subcutaneous belimumab administered in combination with rituximab in adults with systemic lupus erythematosus (SLE): BLISS-BELIEVE study protocol

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- Adhering to the SPIRIT guidelines is recommended and the SPIRIT checklist should be uploaded as part of the submission

Abstract (word count: 298; limit: 300)

Introduction: Belimumab, an anti-B-lymphocyte-stimulator antibody, is approved for the treatment of active, autoantibody-positive systemic lupus erythematosus (SLE). Rituximab, a B-cell-depleting anti-CD20 antibody, remains in the SLE treatment armamentarium despite failed trials in lupus nephritis and extra-renal lupus. These biologics, which operate through complementary mechanisms, might result in an enhanced depletion of circulating and tissue-resident autoreactive B lymphocytes when administered together. Thus, belimumab and rituximab combination may be a highly effective treatment of SLE. This study aims to evaluate and compare the efficacy, safety and tolerability of subcutaneous (SC) belimumab and a single cycle of rituximab in patients with SLE with belimumab alone.

Methods and analysis: BLISS-BELIEVE is a 3-arm, randomised, double-blind, placebo-controlled, 104-week superiority study. Two hundred adults with SLE will be randomised 1:2:1 to Arm A, belimumab SC 200 mg/week for 52 weeks plus placebo at Weeks 4 and 6; Arm B, belimumab SC 200 mg/week for 52 weeks plus rituximab 1000 mg at Weeks 4 and 6; Arm C, belimumab SC 200 mg/week plus standard therapy for 104 weeks. The 52-week treatment period (Arms A and B) is followed by a 52-week observational phase. The primary efficacy endpoint is the proportion of patients with disease control (SLE Disease Activity Index (SLEDAI)-2K ≤2, without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day) at Week 52. Major secondary efficacy endpoints are the proportion of patients in clinical remission (defined as SLEDAI-2K =0, without immunosuppressants and corticosteroids) at Week 64, and the proportion of patients with disease control at Week 104. Safety endpoints include the incidence of adverse events (AEs), serious AEs and AEs of special interest.

Ethics and dissemination: Within 6 months of the study's primary manuscript publication anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Trial registration number: NCT03312907

Article summary (Strengths and limitations of this study)

- This study builds on the experience of randomised controlled trials of the biologics belimumab and rituximab used as single agents, as well as pre-clinical findings, case studies and open-label trials of belimumab and rituximab combination treatment

- The unique sequence of treatment administration, and assessment of the clinically relevant outcomes of disease control and disease remission, are novel features of this study

- BLISS-BELIEVE is the first randomised trial to carry out observations for 52 weeks after stopping belimumab treatment, allowing for the assessment of true disease remission and its durability

- BLISS-BELIEVE randomises patients to a third treatment arm of belimumab plus standard-of-care therapy, to reflect current real-life practice

- The study is limited by a relatively small sample size, and thus has limited power to detect infrequent adverse events

Introduction

Immune-mediated inflammatory diseases (IMIDs) share some common molecular pathways that lead to inflammation, which results from dysregulation of the normal immune response. Chronic inflammation in IMIDs is associated with progressive tissue damage as well as increased co-morbidity and mortality. Systemic lupus erythematosus (SLE) and Sjögren's syndrome are both prototypic antibody-dependent IMIDs.[1] SLE is a chronic multisystem inflammatory autoimmune disease associated with impaired health-related quality of life.[2 3] The ultimate goals of SLE treatment are disease remission, damage prevention (from both disease progression and prolonged use of medication) and normalisation of health-related quality of life.[4 5] These goals are difficult to achieve in most patients owing to limitations in the efficacy of, and long-term toxicity associated with, conventional treatments for SLE, such as corticosteroids and immunosuppressants.[6 7]

Patients with SLE have elevated levels of circulating B-lymphocyte stimulator (BLyS), a member of the tumour necrosis factor ligand superfamily that promotes B cell activation and differentiation.[8-10] Increased serum BLyS levels in patients with SLE are associated with disease activity, disease relapse and increased numbers of autoantibody-secreting plasma cells, linking BLyS to the pathogenesis of SLE.[9 11] Belimumab, a recombinant immunoglobulin G1λ human monoclonal antibody, binds to and antagonises the biological activity of soluble BLyS.[12] It has shown efficacy in patients with autoantibody-positive active SLE in multiple trials.[13-16] Belimumab-treated patients also experienced fewer disease flares, and showed a reduction in steroid use and long-term organ damage accrual compared with patients receiving standard of care (SoC).[13-17] While the efficacy of belimumab has been demonstrated in patients with SLE, a proportion of patients maintain a degree of disease activity despite belimumab treatment.[13-16] Therefore, additional effective and well-tolerated treatment options are required to further improve overall disease control.

Rituximab is a B-cell-depleting, anti-CD20 monoclonal antibody that showed promise in several open-label clinical studies,[18-22] but failed to demonstrate efficacy in two randomised trials in SLE and lupus nephritis.[23 24] In autoimmune diseases, rituximab treatment results in rapid and near complete depletion of circulating CD20+ B cells; however, relatively high numbers of B cells persist in tissues, such as bone marrow, kidneys, synovium and salivary glands.[25-29] In SLE, an increase in BLyS levels after rituximab treatment may contribute to survival and rebound of autoreactive B cells and subsequent disease flares,[30 31] as demonstrated in several cohort studies.[32-34] Consistent with these

observations, reduced maturation of autoreactive B cells during B-cell reconstitution was observed in mice treated with an agent that blocked B-cell activating factor.[35]

Combining belimumab with rituximab therefore has a strong immunological rationale, as the drugs operate through complementary and perhaps synergistic mechanisms.[36] Belimumab treatment results in the mobilisation of memory B cells from tissues despite an overall decrease in peripheral B cell levels.[37] This phenomenon will render tissue-resident B cells more susceptible to depletion by rituximab. In addition, blocking the effects of high serum BLyS levels might have favourable quantitative and qualitative effects on B-cell reconstitution after depletion.[31] Synergistic or additive effects of such a combination have indeed been demonstrated in pre-clinical studies in lupus-prone mice. Improved tissue B-cell subset depletion, a decrease in the levels of autoantibodies, reduced proteinuria and improved survival were observed with combination therapy compared with either treatment alone.[38-40]

This hypothesis is further supported by case reports in patients with SLE, lupus nephritis and Sjögren's syndrome,[41-45] and prompted the SynBioSe study, which showed significant clinical and immunological improvements from baseline in patients with refractory SLE who received rituximab and belimumab.[46] Several clinical trials are currently investigating belimumab and rituximab combination therapy in primary Sjögren's syndrome (NCT02631538), lupus nephritis (CALIBRATE; NCT02260934), and SLE (BEAT Lupus; ISRCTN47873003).

We hypothesised that durable low disease activity might be achieved in patients with active SLE by re-setting the autoreactive humoral immune system. Therefore, we have designed the BLISS-BELIEVE study to examine whether combination treatment with belimumab and rituximab could induce a pre-defined state of disease control or disease remission, allowing the tapering of conventional SLE therapies. This study will employ a novel sequence of belimumab and rituximab combination therapy and investigate novel study endpoints, which could potentially shift the current paradigm of SLE treatment.

The objective of this study is to evaluate the efficacy, safety and tolerability of subcutaneous (SC) belimumab and a single cycle of rituximab administered in a combination regimen in adult patients with SLE compared with belimumab alone.

Methods and analysis

Study design

This is a Phase 3, multicentre, 3-arm, randomised, double-blind, placebo-controlled, 104-week superiority study (BEL205646; NCT03312907). There will be a 52-week double-blind treatment period followed by a 52-week double-blind observational treatment-free follow-up period in Arms A and B (to Week 104) (**Figure 1**). The study began recruitment in March 2018, with an estimated final completion in June 2021.

Study population

Detailed inclusion and exclusion criteria are listed in **Table 1**. Briefly, patients must be ≥18 years of age, with a clinical diagnosis of SLE according to the American College of Rheumatology criteria, and a SLE Disease Activity Index (SLEDAI)-2K score ≥6 at screening. Patients with severe lupus nephritis or severe active central nervous system lupus will be excluded. Informed consent will be obtained from patients prior to the initiation of any study procedures or study-specific data collection.

Randomisation

Patients will be randomised 1:2:1 to one of three treatment arms: belimumab plus placebo (Arm A, control), belimumab plus rituximab (Arm B, combination), or belimumab plus SoC (Arm C, reference). At randomisation, patients will be stratified by their screening SLEDAI-2K score (≤9 vs ≥10), immunosuppressant use (immunosuppressant use vs no use), and corticosteroid dose (prednisone equivalent ≤10 mg/day vs >10 mg/day). Randomisation, and the first dose of belimumab, should be completed within 35 days of the initiation of screening.

Blinding

The study is double-blind with regards to whether participants are randomised to Arm A or Arm B. Randomisation to Arm C will not be blinded. To minimise bias given that Arm C is open-label, independent assessors blinded to treatment group will conduct the SLEDAI-2K assessments at selected visits for the primary and major secondary efficacy endpoints. Unblinded safety data will be reviewed regularly by an Independent Data Monitoring Committee.

Study treatments

Patients randomised to Arm A (control) will receive belimumab SC 200 mg/week for 52 weeks with a cycle of intravenous (IV) placebo (rituximab matched; dose 1 at Week 4 and dose 2 at Week 6). Patients randomised to Arm B (combination) will receive belimumab SC 200 mg/week for 52 weeks

with a cycle of rituximab IV (1000 mg doses given at Week 4 and Week 6). Patients randomised to Arm C (reference) will receive belimumab SC 200 mg/week plus SoC, including immunosuppressants, for 104 weeks. Patients in Arms A and B will be administered a pre-medication regimen 30 minutes before each placebo or rituximab infusion, consisting of methylprednisolone IV 100 mg or equivalent, an oral antihistamine, and acetaminophen or equivalent (**Table 2**).

After completing Week 52, patients in Arms A and B will enter into the 52-week treatment-free (defined as no active treatment with belimumab and/or rituximab), observational phase of the study (Weeks 53 through 104). Patients in Arm C will continue to receive belimumab SC and stable immunosuppressants during this phase. In addition, treatment with antimalarials, non-steroidal anti-inflammatory drugs, and corticosteroids (prednisone equivalent ≤5 mg/day) is allowed in the observational phase in all three arms.

Patients considered treatment failures (patients in Arm A or B who fail to respond adequately to study treatment, who do not meet the corticosteroid taper rules or tolerate immunosuppressant withdrawal at Week 4, or who require additional therapy) will be encouraged to remain in the study to receive all safety and efficacy assessments through Week 104. During this time (Weeks 53–104), additional treatment may be given, if deemed of benefit by the investigator, to patients with responses that do not reach the predefined study criteria for disease control (as defined in the study endpoints), or subsequently experience increased disease activity. This treatment can include belimumab, corticosteroids, and/or immunosuppressants; additional treatment with rituximab will be permitted, but not encouraged.

Concomitant medications

Patients randomised to Arms A and B who enter the study on immunosuppressants will discontinue immunosuppressants at or prior to the Week 4 visit. Patients in Arm C who enter the study on stable immunosuppressants may continue to receive them throughout the study. After the initial 12 weeks of study treatment, a protocol-specified corticosteroid taper will be initiated for all three arms (carried out under direction of the investigator), with a target of reaching a prednisone equivalent dose of ≤5 mg/day by Week 26. After Week 26, if a patient's average daily corticosteroid dose exceeds 5 mg/day prednisone equivalent, the patient will be declared a treatment failure. Antimalarials and non-steroidal anti-inflammatory drugs may be used throughout the study for all treatment arms.

Other investigational agents (or co-enrolment into another study of a different investigational agent), anti-tumour necrosis factor therapy, other biologics with effects on the immune system, immunoglobulin IV, cyclophosphamide IV, and plasmapheresis are prohibited throughout the study.

Study endpoints

The primary efficacy endpoint is the proportion of patients with disease control at Week 52, defined as a SLEDAI-2K score of ≤2, achieved without immunosuppressants and with a prednisone equivalent dose of ≤5 mg/day. The major secondary efficacy endpoints are the proportion of patients in clinical remission at Week 64 (defined as a clinical SLEDAI-2K score of 0, allowing for serologies of anti-dsDNA and hypocomplementemia and achieved without immunosuppressants and corticosteroids), and the proportion of patients with disease control at Week 104 (defined as a SLEDAI-2K score of ≤2, achieved without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day). Patient reported outcome measures include change from baseline in Patient Global Assessment (PtGA), LupusQoL domain summary scores, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score, and proportion of patients with an improvement in FACIT-Fatigue score exceeding the minimal clinically important difference. Safety endpoints include the incidence of adverse events (AEs), including serious AEs (SAEs) and AEs of special interest (AESI). The endpoints will be assessed using the measures listed in **Table 3**.

Sample size calculation

Approximately 400 patients will be screened, with a goal of randomising at least 200 patients (50% screen failure rate). A target of 50 patients will be randomised in Arms A and C, and 100 patients in Arm B. This sample size provides at least 95% power (for the comparison of Arm B to Arm A at Week 52) at a 5% level of significance, assuming the underlying response in the control arm is 10%, and the true population effect is ≥25% with treatment Arm B (assumed response rate of 35%). For the primary endpoint, patients who drop out from the study will be included in the analysis as non-responders; thus, the assumed responder rates for Arms A and B already account for the rate of patient dropout. However, to ensure adequate safety exposure in Arm B, the sample size may be increased up to 300 patients if the dropout rate reaches 10% at the scheduled time point for receiving both doses of placebo or rituximab.

Based on limited clinical data with therapies including both belimumab and rituximab, opinions from external experts, and the rarity of remission or disease control seen in published studies, a rate of 35% of patients in Arm B achieving a state of disease control is considered to be highly clinically

significant in SLE care. A response rate of 10% at Week 52 was assumed for Arm A (control), based on historical data from three belimumab Phase 3 trials. Assuming a 10% control responder rate and 50 patients in Arm A and 100 patients in Arm B, the minimum detectable effect at $p<0.05$ is a 12% improvement (i.e., an observed improvement of 12% or more in Arm B would give a $p<0.05$). A sample size sensitivity analysis was conducted on the primary endpoint to investigate the impact on power if the assumed underlying control response rate deviates from 10% or the treatment difference deviates from 25%.

Statistical analyses

Unless otherwise stated, all analyses will be performed on the intent-to-treat population. The key analyses will compare belimumab with or without a single cycle of rituximab (Arm A vs Arm B). Descriptive statistics will be used to compare the combination of belimumab with a single cycle of rituximab (Arm B) versus belimumab with SoC (Arm C). The primary and major secondary endpoints will be compared using a logistic regression model. The independent variables will include treatment group, baseline SLEDAI-2K score (≤9 vs ≥10), immunosuppressant use at baseline (immunosuppressant use vs no use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs >10 mg/day). If any factor fails to converge it will be removed from the logistic model. If the model fails to converge (e.g. owing to a small number of responders), the endpoints will be analysed using a Fisher's exact test. Missing data are accounted for in the primary efficacy endpoint, as all patients will be classified as either a non-responder (including premature study discontinuation or treatment failure prior to Week 52) or responder. Sensitivity analyses will be used to explore the impact of missing data and treatment failure imputation. Descriptive statistics will be used to summarise AEs, SAEs, AESI, changes in laboratory parameters, and immunogenicity.

Ethical considerations

This study will be conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines, applicable International Conference on Harmonisation Good Clinical Practice Guidelines, and applicable laws and regulations. The protocol has been reviewed and approved by institutional review boards (IRB)/independent ethics committees (IEC). The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. SAEs will be reported by the investigator to the sponsor immediately, and no later than within 24 hours. Written

informed consent will be obtained from all patients, who will be assigned a unique identifier; all patient records and data transferred to the sponsor will contain the identifier only.

Dissemination

Study information will be publicly available at www.clinicaltrials.gov, and the results of this trial (positive and negative) will be submitted for publication in relevant peer-reviewed publications and the key findings presented at national and international conferences. Within 6 months of the publication of the primary manuscript for this study, anonymised individual participant data, the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset, and clinical study report will be available for research proposals approved by an independent review committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access agreement will be required. This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations for protocol reporting.[47]

Patient and public involvement

Patients and/or public were not involved in the development of this study.

Discussion

This study aims to explore the potential for synergy and to demonstrate greater efficacy of combination treatment with belimumab and rituximab compared with belimumab monotherapy in achieving low disease activity, disease remission, or clinical quiescence in patients with SLE. Although to date, combination biologics have not been widely used in other diseases, we think there is a strong immunological rationale to study belimumab and rituximab combination therapy in the context of SLE. The residual disease activity that many patients with SLE experience despite current therapies, further justifies the exploration of this novel combination treatment. If this study confirms our hypothesis that combined belimumab and rituximab treatment has additional efficacy over standard belimumab care, then this may transform the current treatment paradigm, allowing patients with SLE to discontinue conventional, often toxic medications.

The unique sequence of administering belimumab and rituximab (which we believe will enhance B cell depletion), the use of belimumab SC and a larger sample size, differentiate the BLISS-BELIEVE study from BEAT Lupus (ISRCTN47873003),[48] a similar belimumab and rituximab combination

therapy, Phase 2 trial in SLE that is currently recruiting patients in the UK. The sequence of treatment administration also differs from that used in the CALIBRATE trial in lupus nephritis (NCT02260934).[49] In addition, BLISS-BELIEVE is one of the first trials of belimumab to carry out assessments for 52 weeks after stopping treatment, and investigate ambitious, clinically relevant outcomes of low disease activity or disease remission. The 52-week observational, treatment-free phase provides an opportunity to observe if a true disease remission occurs, and allows for the assessment of the durability of any such remission or low disease activity. In the treatment of SLE, it is important to balance clinical efficacy and therapy-related toxicity. The unique design of BLISS-BELIEVE will ensure this is assessed through the use of rigorous endpoints (such as clinical remission), and by enabling the termination of belimumab if toxicity is an issue.

The unique treatment schedules were selected according to a rationale based on the current evidence. In the 52-week treatment phase, belimumab SC 200 mg will be administered weekly as per the treatment regimen in the Phase 3 study of belimumab SC, which demonstrated its safety and efficacy in patients with SLE.[15] Rituximab is not approved for the treatment of patients with SLE, and no standard dosing regimen has been established. Based on previous trials of rituximab that showed a lack of efficacy, we deemed that a rituximab-only arm would fail to meet standards of equipoise. In the current study, rituximab dosing will follow one cycle of the approved dosing recommendation for rheumatoid arthritis, which is two doses of 1000 mg IV given 2 weeks apart. In a Phase 2/3 trial, this rituximab regimen demonstrated rapid depletion of CD19-positive cells (<5 cells/μL) in the majority of patients with SLE.[23] It is also the dosing regimen recommended in NHS England's Interim Clinical Commissioning Policy Statement for rituximab use in patients with refractory SLE.[50] Furthermore, belimumab and rituximab combination treatment has previously shown acceptable safety and significant clinical responses in patients with severe, refractory SLE.[46]

Separating the administration of belimumab and rituximab may allow for observation of safety events attributable to each treatment; however, owing to the relatively small sample size, the study will have limited power to detect less common AEs. With the consecutive administration regimen, the study allows investigation of the hypothesis that belimumab mobilises additional CD20+ B cells into the circulation, making them available for anti-CD20 treatment with rituximab. Therefore, we will be able to further establish whether more efficient depletion of autoreactive B cells, otherwise protected from cell death in the tissue niches, is achieved.[37] We anticipate that there will be fewer autoreactive B cells appearing in the memory B-cell compartment during the early phase of B-cell reconstitution. However, we are aware that the controls for this analysis are historical, owing to the

ethical considerations discussed above. B-cell mobilisation will be evaluated by comparing baseline, pre-belimumab B-cell levels with autoreactive B cells appearing in peripheral blood after belimumab treatment. The possible reappearance of autoreactive B cells following rituximab treatment will then be established by comparing B cells levels between the belimumab only and belimumab and rituximab arms.

This study has some limitations. Because rituximab is not approved for the treatment of patients with SLE, a rituximab-only arm could not be included in the protocol. Therefore, some clinical and serological outcomes attributable to rituximab treatment will not be assessed. However, this study aims to explore whether belimumab treatment can be optimised by sequential treatment with rituximab, for which a rituximab-only arm is not required. Another limitation of the study design is that direct measurements of B-cell depletion in tissue niches will not be performed. However, this measurement and a rituximab-only arm are being explored in a clinical trial of belimumab and rituximab combination therapy in primary Sjögren's syndrome (NCT02631538), which follows a similar administration regimen. Another concern is that patients in Study Arms A and B will discontinue immunosuppressants from Week 4, which might result in a higher than predicted treatment failure rate, due to flares occurring before belimumab and rituximab achieve therapeutic efficacy at Week 12. However, the risk of disease flares to patients will be mitigated by methylprednisolone pre-treatment and the option for investigators to adjust concomitant corticosteroid treatment as clinically necessary up to Week 26. Although substantially different from previous belimumab trials, such as BLISS 76, in which more than half the patients continued on background immunosuppressive agents,[12] this regimen will allow investigation of whether belimumab and rituximab combination therapy could result in an immunologically more favourable condition in some patients, thus enabling the tapering of conventional immunosuppressive drugs and possibly an immunosuppressant-free honeymoon. A positive outcome of BLISS-BELIEVE would further support the rationale to test this therapeutic strategy in Sjögren's syndrome and other autoantibody-dependent IMIDs.

In conclusion, the BLISS-BELIEVE study is supported by strong scientific rationale from pre-clinical studies, case reports and open-label trials. Its pioneering and unique design will allow for a long-term observation of true clinical remission, assessment of the durability of such a remission state, and assessment of any potential safety issues. The results of this study may support the rationale for combination therapy in other autoimmune conditions. BLISS-BELIEVE began recruitment in March 2018, with estimated study completion in June 2021.

Contributors:

PPT initiated this study and has been involved in its design. **YKOT, INB, RAF, RFvV, DG, JG, RBH, MO,** and **PPT** were involved in the development of the study protocol, preparation of the manuscript and its subsequent revisions, and provided final approval of the version published. **BD** was involved in the preparation of the manuscript and its subsequent revisions, and provided final approval of the version published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests:

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Ethics approval: The protocol has been approved by IRB/IEC. Each study site has obtained relevant IRB/IEC approvals.

Figure 1: Study design

IV, intravenous; PBO, placebo; RTX, rituximab; SC, subcutaneous; SoC, standard-of-care; W, week

Table 1: Patient inclusion and exclusion criteria

Inclusion criteria
≥18 years of age
Clinical diagnosis of SLE according to the ACR criteria
Minimum screening SLEDAI-2K score ≥6
Unequivocally positive ANA and/or anti-dsDNA test results from two independent time points
Stable SLE treatment regimen
Female patients not pregnant, not breastfeeding, not of childbearing potential or follow contraceptive guidance
Exclusion criteria
Symptomatic herpes zoster within 3 months prior to screening
Active or latent TB, confirmed by medical history and examination, chest X-rays, and TB testing: either a positive TST (defined as a skin induration ≥5 mm at 48–72 hours, regardless of BCG or other vaccination history), or a positive QuantiFERON-TB Gold test
Allergies to humanised monoclonal antibodies
Clinically significant multiple or severe drug allergies and/or history of hypersensitivity to belimumab and/or rituximab
Lymphoma, leukaemia, or any malignancy within the past 5 years
ALT >2x ULN
Bilirubin >1.5x ULN
IgA < 10 mg/dL
IgG < 250 mg/dL
Neutrophils < 1.5 x 10^9
Unstable liver or biliary disease
Severe heart failure
QTc >450 msec or >480 msec in patients with bundle branch block
History of a major organ transplant
Clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE
Acute or chronic infection requiring management
Severe lupus kidney disease
Severe active central nervous system lupus
Planned surgical procedure, laboratory abnormality, or condition that makes the patient unsuitable for the study
Evidence of serious suicide risk
History of an anaphylaxis reaction to parenteral administration of contrast agents, human/murine proteins, or monoclonal antibodies
Live vaccine(s) within 1 month prior to screening
Within 364 days of Day 1, received certain biologics (belimumab, rituximab, abatacept, a B-cell-targeted therapy, a biologic investigational agent other than B-cell-targeted therapy), or required 3 or more courses of systemic corticosteroids
Within 90 days of Day 1, received anti-TNF therapy, interleukin-1 receptor antagonist, intravenous immunoglobulin, high-dose prednisone or equivalent, or plasmapheresis
Within 60 days of Day 1, received a non-biologic investigational agent, intravenous cyclophosphamide, a steroid injection

Positive HIV antibody test
Positive serology for hepatitis B or hepatitis C
Current or history (within 364 days of Day 1) of drug/alcohol dependence
Sensitivity to any of the study treatments or components
Unable to administer belimumab by SC injection

ACR, American College of Rheumatology; ALT, alanine aminotransferase; ANA, anti-nuclear antibodies; BCG, Bacillus Calmette-Guerin; IgA, immunoglobulin A; HIV, human immunodeficiency virus; IgG, immunoglobulin G; SC, subcutaneous; QTc, corrected QT; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index; TB, tuberculosis; TNF, tumour necrosis factor; TST, tuberculin skin test; ULN, upper limit of normal

Table 2: Study treatment arms

Treatment	Arm A (control)	Arm B (combination)	Arm C (reference)
Belimumab	Belimumab SC 200 mg/week for 52 weeks	Belimumab SC 200 mg/week for 52 weeks	Belimumab SC 200 mg/week plus SoC for 104 weeks
Rituximab or matched placebo	One cycle of placebo IV (rituximab matched) at Week 4 and Week 6	One cycle of rituximab IV 1000 mg at Week 4 and Week 6	None
Pre-medication (30 minutes before each placebo or rituximab infusion)	Methylprednisolone IV 100 mg or equivalent, oral antihistamine, acetaminophen or equivalent	Methylprednisolone IV 100 mg or equivalent, oral antihistamine, acetaminophen or equivalent	None
Post Week 52 therapy	Antimalarials, NSAIDs, and/or corticosteroids with a prednisone equivalent dose of ≤5 mg/day	Antimalarials, NSAIDs, and/or corticosteroids with a prednisone equivalent dose of ≤5 mg/day	Continue belimumab SC 200 mg/week plus SoC[a]

[a]Patients in Arm C are allowed to receive rescue therapy if, in the opinion of the investigator, they require additional treatment. This can include corticosteroids at >5 mg/day prednisone equivalent

IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; SC, subcutaneous; SoC, standard-of-care

Table 3: Study assessments

Efficacy assessment
SLEDAI-2K, a clinical index for measuring SLE disease activity in the previous 10 days, at screening/baseline and at Weeks 52, 64 and 104
Safety assessment
Full physical examination, electrocardiogram, clinical safety laboratory assessments, neurological assessment, and suicidal risk monitoring (assessed via C-SSRS) at screening. Symptom-driven physical examination, vital signs, clinical safety laboratory assessments, neurological assessment, and suicidal risk monitoring at scheduled and unscheduled visits
Laboratory tests
Anti-dsDNA/ANA, complement C3/C4, serum immunoglobulin (IgG, IgA, IgM), urine testing (urinalysis, spot urine protein), haematology and blood chemistry, pregnancy test: performed at screening and at each assessment visit. Autoantibody levels, including aCL, beta-2-glycoprotein, lupus anticoagulant, and extractable nuclear antigens, will be measured at Day 1 and Weeks 8, 26, 52, 60, 80, and 104
B-cell analyses
Pharmacokinetics

aCL, anti-cardiolipin; ANA, anti-nuclear antibodies; C, complement; C-SSRS, Columbia-Suicide Severity Rating Scale; Ig, immunoglobulin; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLE, systemic lupus erythematosus

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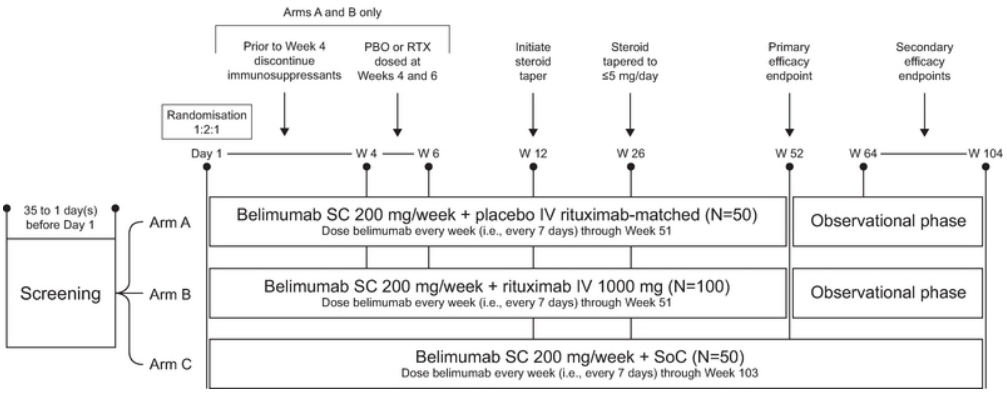

Study Design
IV, intravenous; PBO, placebo; RTX, rituximab; SC, subcutaneous; SoC, standard-of-care; W, week

67x25mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number in the manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_2 and 6_____
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (protocol p.1)
Protocol version	3	Date and version identifier	Yes (protocol p.1)
Funding	4	Sources and types of financial, material, and other support	_____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1 and 15_____
	5b	Name and contact information for the trial sponsor	Yes (protocol p.1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__15–16____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Yes (protocol p.99)

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4–5_____
	6b	Explanation for choice of comparators	___13–14____
Objectives	7	Specific objectives or hypotheses	___5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Listed in the clinicaltrials.gov record
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__6–7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___8–9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Yes (protocol p.58)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___9–10_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___10–11_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_23 (Figure 1)_
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____N/A_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Yes (protocol p.56)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Yes (protocol p.56)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Yes (protocol p.56)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Yes (protocol p.56)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Yes (protocol p.57)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Yes (protocol p.100)

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____7_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Yes (protocol p.100)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____9_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____9_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Yes (protocol p.99)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Yes (protocol p.88)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____9–10_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Yes (protocol p.88)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____9_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Yes (protocol p.98)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Yes (protocol p.98)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____9–10_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___13_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Yes (protocol p.88)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___10_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___13_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___10_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__No_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes (protocol)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.