PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Teng, Y.K Onno; Bruce, Ian; Diamond, Betty; Furie, Richard; van Vollenhoven, Ronald; Gordon, David; Henderson, Robert; Groark, James; Oldham, Mary; Tak, Paul

VERSION 1 – REVIEW

REVIEWER	Daniel J Wallace MD Cedars-Sinai Medical Center, Los Angeles, CA
REVIEW RETURNED	24-Aug-2018

GENERAL COMMENTS	This is a very timely, much needed study intended to address whether mobilitzation of CD20+ T cells into the circulation with belimumab makes them more available for anti CD20 treatment with rituximab and takes into account the negative effects of increasing soluble BlyS after rituximab treatment.. I have a few comments which may warrant addressing or special consideration: 1. There is no restriction on entry corticosteroid dosing. Using high doses of this agent may make it more difficult to look for change with the treatment protocol (e.g., EXPLORER, LUNAR). 2. At any given visit, work by Matt Liang has suggested that only 15% of all US lupus patients have a SLEDAI of 6 or greater at any clinic visit. It will be difficult to screen 400 patients over 3 years meeting entry criteria (excluding severe renal patients as well) unless community sites in non-academic, non-US or non-Western Europe are included. 3. Since patients are being administered rituximab in a high dose 2 weeks apart, there is no fail safe for checking the CBC or CD19/20 levels prior to the second dose. 4.IgG subclass 4 in particular is decreased with rituximab and associated with more infections, and IgG subclasses are not measured. 5. There will be more flares in the arm where immune suppressants are discontinued, since both belimumab and rituximab will not achieve their greatest therapeutic efficacy for 12 weeks. I am particularly concerned about those with mild renal disease who stop mycophenolate flaring at week 6-10, which is confounding. 6. BILAG should be measured, so that post hoc analyses can include SRI-4, etc, determinations. 7. No patient reported outcome measures are included. 8. There is no demographic, geographic, or racial stratification. 9. Mandated steroid tapering for all comers using the same regimen regardless of organ specific involvement is artificial and

	lumps those with active synovitis, autoimmune hemolytic anemia and other co-morbidities into the same silo. Its not how rheumatologists practice lupology.

REVIEWER	Yoshiya Tanaka, MD University of Occupational and Environmental Health, Japan, First Department of Internal Medicine
REVIEW RETURNED	02-Sep-2018

GENERAL COMMENTS	The authors reported a phase study protocol of BLISS-BELIEVE study, multicentre, randomised, double-blind, placebo-controlled, 104-week study of SC belimumab administered in combination with rituximab in patients with SLE. The primary endpoint is the proportion of patients with disease control at Week 52 and secondary endpoints are the proportion of patients in clinical remission at Week 64 and disease control at Week 104 for 52 weeks after stopping belimumab treatment. Although it is an interesting study, some issues are to be addressed. 1. The study includes an Arm C of belimumab plus SoC. Is it possible to do it as a “double-blinded” manner? Is it “semi-double-blind”? 2. The primary endpoint is the proportion of patients with disease control at Week 52, mainly comparing with or without rituximab under the background belimumab. It appears a RTX-BELIEVE study. 3. It is novel and interesting to carry out observations for 52 weeks after stopping belimumab treatment. Is it necessary to set post week 52 therapy of the Arm C of belimumab with PSL equivalent dose of ≤5 mg/day as do in arms A and B.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Daniel J Wallace MD, Cedars-Sinai Medical Center, Los Angeles, CA)
This is a very timely, much needed study intended to address whether mobilization of CD20+ T cells into the circulation with belimumab makes them more available for anti CD20 treatment with rituximab and takes into account the negative effects of increasing soluble BlyS after rituximab treatment. I have a few comments which may warrant addressing or special consideration:

1. There is no restriction on entry corticosteroid dosing. Using high doses of this agent may make it more difficult to look for change with the treatment protocol (e.g., EXPLORER, LUNAR).

RESPONSE: The reviewer is correct that entry corticosteroid dose is not restricted. However, patients will be stratified based on their corticosteroid dose at baseline (prednisone equivalent ≤10 mg/day vs >10 mg/day); this is included as an independent variable in the logistic regression model that will be used for the primary and major secondary efficacy endpoints. Also, in order to meet the criteria for disease control (primary endpoint) and clinical remission (secondary endpoint), patients have to achieve the relevant SLEDAI scores without corticosteroids, or with a prednisone equivalent dose of ≤5 mg/day, respectively.

Additionally, after 12 weeks of treatment, a protocol-specified corticosteroid taper scheme will be initiated, 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.

For these reasons, we believe that any potential effects of corticosteroid dose at baseline have been taken into account in the study design and data analyses. To clarify, we have included additional information on the taper scheme in the 'Concomitant medications' section of the Methods (information on the endpoints and statistical analyses are already included):

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.

2. At any given visit, work by Matt Liang has suggested that only 15% of all US lupus patients have a SLEDAI of 6 or greater at any clinic visit. It will be difficult to screen 400 patients over 3 years meeting entry criteria (excluding severe renal patients as well) unless community sites in non-academic, non-US or non-Western Europe are included.

RESPONSE: Countries with participating study sites include Argentina, Brazil, South Korea, and the Russian Federation, in addition to those in North America and Western Europe. So far, there are 77 participating centres across 10 countries. We believe that this will be sufficient to screen 400 patients. We are expecting a ~50% screen failure rate, so the target for randomisation is 200 patients (as stated in the sample size calculation section of the manuscript). To date, patient enrolment with the current entry criteria has been brisk with no evidence of slowing, and we are on track to achieve the target patient number. We cannot include any enrollment numbers in the manuscript as these may change pending regulatory interaction.

3. Since patients are being administered rituximab in a high dose 2 weeks apart, there is no fail safe for checking the CBC or CD19/20 levels prior to the second dose.

RESPONSE: As rituximab is not approved for SLE, the rituximab administration schedule in this study is designed to follow one cycle of the approved dosing recommendation for rheumatoid arthritis, (two doses of 1000 mg IV given 2 weeks apart). As mentioned in the Introduction and Discussion, results for this rituximab regimen in two cycles have been reported previously by the EXPLORER and LUNAR trials in patients with SLE and lupus nephritis, respectively. These studies showed profound and prolonged B-cell depletion in approximately 10% of patients without apparent increase in the rate of serious infections. This is in addition to the extensive safety data on the use of this rituximab regimen in rheumatoid arthritis. However, we are mindful that there are limited data on rituximab and belimumab in combination, and for this reason a benefit/risk assessment of available data, including data from the GSK safety database, ongoing studies of rituximab and belimumab in combination, and the Safety Works insurance claims database, was performed. Based on this, no new safety risks are expected with the combination therapy. Nevertheless, a set of robust safety monitoring and stopping rules have been developed and included in the study protocol to safeguard patient safety, with a detailed mitigation strategy for each potential risk identified. Furthermore, please note that a substudy of B cell depletion is planned in patients with SLE, however, this was not a key endpoint of the current trial.

4. IgG subclass 4 in particular is decreased with rituximab and associated with more infections, and IgG subclasses are not measured.

RESPONSE: As samples will be stored, it should be possible to measure IgG subclasses in the future; thank you for this helpful suggestion.

5. There will be more flares in the arm where immune suppressants are discontinued, since both belimumab and rituximab will not achieve their greatest therapeutic efficacy for 12 weeks. I am particularly concerned about those with mild renal disease who stop mycophenolate flaring at week 6-10, which is confounding.

RESPONSE: Please note that discontinuation of immune suppressants was included in the design of the study in order to better demonstrate any early effects of study medication. All patients will be closely monitored and treatment adjustment will be critical to mitigating the risk of disease flares in this period. We expect therapeutic benefit from premedication with methylprednisolone IV 100 mg prior to rituximab or placebo infusion. Patients will also enter the study on their prescribed corticosteroid dose and investigators can adjust the dose as clinically necessary through to Week 26. If required, immunosuppressants can be reinitiated and, although this will trigger treatment failure, these patients will remain on study and continue to undergo all efficacy and safety assessments.

In response to your concerns, we have now revised the wording in the Discussion for clarity:

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.

6. BILAG should be measured, so that post hoc analyses can include SRI-4, etc, determinations.

RESPONSE: SLEDAI-2 K was chosen as the measurement of disease activity in this study, as it is one of the most commonly used global disease activity measures in longitudinal observational studies and clinical trials (Mikdashi and Nived. *Arthritis Res Ther* 2015; 17:183). We understand that the lack of BILAG assessments will limit the ability to assess composite indices in post hoc analyses, however, it was not possible to include every outcome measure of interest for practical reasons.

7. No patient reported outcome measures are included.

RESPONSE: In order to keep the manuscript concise, we only included primary and major secondary outcomes. The study protocol does include the following patient-reported outcomes: Patient Global Assessment (PtGA), LupusQoL domain summary scores, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score (including proportion of patients with an improvement in FACIT-Fatigue score exceeding the Minimal Clinically Important Difference). We have now added these outcomes to the 'Study endpoints section of the Methods:

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.

8. There is no demographic, geographic, or racial stratification.

RESPONSE: Stratification is usually only indicated if the variable is deemed to be of direct influence on the primary endpoint. We are unaware of data showing that demographic, geographic or racial

variables influence clinical outcomes with rituximab in combination with belimumab in SLE. Clinical variations according to race have been observed previously in SLE trials and, since patient demographics will be recorded, there will be the potential to include these variables in post hoc analyses if deemed appropriate.

9. Mandated steroid tapering for all comers using the same regimen regardless of organ specific involvement is artificial and lumps those with active synovitis, autoimmune hemolytic anemia and other co-morbidities into the same silo. Its not how rheumatologists practice lupology.

RESPONSE: We acknowledge that mandated corticosteroid tapering does not reflect current general clinical practice for SLE. Based on preclinical and preliminary clinical data, we are predicting substantial effects that will allow patients to taper much faster than is currently possible. While the study protocol includes a recommended corticosteroid tapering schedule, this will be subject to investigator discretion and will be conducted under the direction of the investigator. This has been clarified in the 'Concomitant medications' section of the Methods:

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.

Reviewer 2 (Yoshiya Tanaka MD, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan)

The authors reported a phase study protocol of BLISS-BELIEVE study, multicentre, randomised, double-blind, placebo-controlled, 104-week study of SC belimumab administered in combination with rituximab in patients with SLE. The primary endpoint is the proportion of patients with disease control at Week 52 and secondary endpoints are the proportion of patients in clinical remission at Week 64 and disease control at Week 104 for 52 weeks after stopping belimumab treatment. Although it is an interesting study, some issues are to be addressed.

1. The study includes an Arm C of belimumab plus SoC. Is it possible to do it as a "double-blinded" manner? Is it "semi-double-blind"?

RESPONSE: The study is double-blind only with regard to Arm A (control) and Arm B (combination). Randomisation to Arm C (reference), which represents current standard of care treatment, will not be blinded. Absence of blinding for Arm C was agreed with regulatory authorities based on logistical difficulties generated by the large same size of this study. In order to minimise bias given that Arm C is open-label, independent assessors blinded to treatment group (A, B, or C) will conduct the SLEDAI-2K assessments at selected visits, including those that are components of the primary and major secondary endpoints. This is stated in the manuscript in the 'Blinding' section of the Methods.

2. The primary endpoint is the proportion of patients with disease control at Week 52, mainly comparing with or without rituximab under the background belimumab. It appears a RTX-BELIEVE study.

RESPONSE: The objective of this study is to establish whether belimumab in combination with rituximab is superior to belimumab alone (as stated at the end of the Introduction). The study was designed in this way as there is a strong immunological rationale for combination therapy with both

agents, as described in the Introduction. The 'BLISS' acronym refers to 'Study of Belimumab in Subjects with SLE'; the BLISS-BELIEVE study was designed based on information yielded from the pivotal BLISS-52 and BLISS-76 studies, with 'BELIEVE' representing RTX.

3. It is novel and interesting to carry out observations for 52 weeks after stopping belimumab treatment. Is it necessary to set post week 52 therapy of the Arm C of belimumab with PSL equivalent dose of ≤5 mg/day as do in arms A and B.

RESPONSE: Patients in Arm C (reference) 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, although this would trigger treatment failure. Therefore, as intended. Arm C best reflects current clinical practice with belimumab for patients with SLE, and inclusion of steroid tapering in this treatment arm allows for comparison between the study treatment arms. Indeed, this is the first study to include a mandated steroid taper with ongoing belimumab treatment, which may provide additional clinical insights as a result.

As stated in the 'Study treatments' section of the Methods, other treatments are allowed during the observational period, including antimalarials and non-steroidal anti-inflammatory drugs, and patients in Arm C will continue to receive belimumab and stable immunosuppressants (at the discretion of the investigator). We have added a footnote to Table 2 for further clarity:

[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*