Addition of Belimumab to B cell depletion to produce prolonged remission of relapsing-remitting multiple sclerosis disease activity

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1. Abstract

Multiple sclerosis is the most common inflammatory disease of the central nervous system and a common cause of disability in young adults. Depleting B cells from the circulation with anti-CD20 antibodies has proven to be an effective strategy in reducing relapses and disability in patients with the relapsing-remitting disease. However, continuous and long-term depletion of B-cells can result in reduced immunoglobulin levels, immunosuppression and increased tendency for severe infections and perhaps, even malignancy. Blocking B-cell Activating Factor (BAFF) is effective for the treatment of several autoimmune disorders. Belimumab, a BAFF blocking antibody, has been approved by the Food and Drug Administration for the treatment of systemic lupus erythematosus. Belimumab has been shown to have immunomodulatory properties, without resulting in overt immunosuppression.
We hypothesize that belimumab, given to patients who received a short course of treatment with B-cell depleting antibody (ocrelizumab), will be safe and equally effective in reducing MS disease activity (as compared to patients receiving continuous treatment with ocrelizumab); while resulting in less immunosuppression, as measured by antibody response to pneumococcal vaccination. Currently, available treatment strategies in relapsing MS sacrifice higher efficacy for long-term safety or vice versa. The proposed strategy in this application combines the long-term safety and high efficacy to treat patients with RRMS and if eventually proven effective, can be adopted in a large proportion of patients with this chronic disease.

2. Objectives

Objectives	Endpoints
Co-primary	
Pneumococcal vaccine antibody response: To estimate the difference between the pneumococcal titer in the serum four weeks after immunization with a 23-valent pneumococcal vaccine administered at month 24 of the study	The proportion of patients with positive antibody responses to >=1 of the 23 pneumococcal vaccine serotypes measured four weeks post-vaccination. A positive antibody response is defined as a two-fold increase from pre-vaccination levels against >=1 of the 23 pneumococcal serotypes measured.

Safety: To assess the difference in safety and tolerability between the two treatment groups at month 24	AEs and SAEs, including AEs of special interest (opportunistic infections, herpes zoster, malignancies, hypersensitivity and infusion reactions, suicidal ideation, intent or behavior and all-cause mortality); Incidence and severity of all infections and serious infection; all assessed by month 24
Secondary and Exploratory	
To assess the difference in safety and tolerability between the two treatment groups at month 36	AEs and SAEs, including AEs of special interest (opportunistic infections, herpes zoster, malignancies, hypersensitivity and infusion reactions, suicidal ideation, intent or behavior, and all-cause mortality); Incidence and severity of all infections and serious infection; Change from baseline and number of subjects outside the normal range for clinical chemistry and hematology parameters, with particular attention to white blood cell count and immunoglobulin levels; all assessed by month 36
To estimate the difference between the two treatment groups in pro / anti-inflammatory cytokine ratio of repopulating B-cells at month 36	GM-CSF/IL-10 and IL-6/IL-10 ratio (produced by stimulated repopulated B-cells at month 36.

Assessment of return of disease activity by month 24 and 36	Return of the disease activity, as objectively demonstrated by development of new T2 hyperintense lesions or Gd-enhancing lesions on the MRI (noted on a scan performed more than six months after treatment initiation) or a clinical relapse, defined as new or worsening neurologic symptom(s) with an objective change on the EDSS of at least 1.5 points for participants with baseline EDSS scores of 0 or 0.5 and at least 1-point change for participants with EDSS of 1 or more, as determined by the examining neurologist. Symptoms must have been attributable to MS, last ≥48 hours, been present at normal body temperature, and preceded by at least 30 days of clinical stability.
Assessment of clinical disease activity by month 24 and 36	Annualized relapse rate (ARR) by month 24 and 36. A clinical relapse is defined as new or worsening neurologic symptom(s) with an objective change on the EDSS of at least 1.5 points for participants with baseline EDSS scores of 0 or 0.5 and at least 1-point change for participants with EDSS of 1 or more, as determined by the examining neurologist. Symptoms must have been attributable to MS, last ≥48 hours, been present at normal body temperature, and preceded by at least 30 days of clinical stability.
Assessment of disability progression by month 24 and 36	Change in MSFC at month 24 and 36 as compared to baseline
	Three-month confirmed increase in EDSS by month 24 and 36
	Three-month confirmed decrease in EDSS by month 24 and 36
Assessment of radiological disease activity by month 24 and 36	Presence of any new Gd-enhancing lesions on an MRI obtained after the baseline
	Presence of any new or enlarging T2 lesions on an MRI compared to the MRI obtained at month 6
Assessment of a serum biomarker of neuroaxonal degeneration by month 24 and 36	Change in serum NfL at month 24 and 36 compared to baseline

Analysis of B cell sub-populations and T cell function	Change in naïve, transitional and memory B cells from baseline to month 24 and 36 Change in the expression of co-stimulatory and antigen presentation molecules on B cells from baseline to month 24 and 36 Change in T cell memory subsets and pro-inflammatory cytokine production (Th1 & Th17) from baseline to month 24 and 36

3. Background

Multiple sclerosis is the most common inflammatory disease of the central nervous system[1]. The antibody-independent pathogenic role of B-cells in multiple sclerosis (MS) has been clearly demonstrated by a profound and rapid cessation of inflammatory disease activity in patients with MS who receive B-cell depleting anti-CD20 monoclonal antibodies[2]. Currently, the standard of care is to indefinitely continue B-cell depleting therapies in MS since we do not know whether a sustained remission of disease activity can be attained with a limited duration of B cell depletion. This approach, while providing high efficacy, in terms of preventing disease relapses, is also associated with greater risks such as infections and malignancy[2,3].

However, some previous data suggest that a prolonged remission may be possible following a short course of B cell depletion, and one hypothesis for this effect of B-cell depletion is that reconstituting B-cells demonstrate a decrease in pro-inflammatory (IL-6 and GM-CSF) and an increase in anti-inflammatory (IL-10) cytokine production[4]. This shift in B cell phenotype has effects on both the myeloid and T cell compartments and could prevent relapse of disease activity even after B cell reconstitution[5]. Studies demonstrating this shift observed these changes in early reconstitution – at which time the balance of naïve to memory B cells had been shifted towards the former, possibly explaining the skewed cytokine profiles (since inflammatory cytokines are predominantly produced by memory B cells). Long-term data post B cell cessation is lacking, and hence it is unclear whether memory cells that produce GM-CSF and IL-6 would eventually return and lead to new inflammatory disease activity.

BAFF is critical for the proliferation and development of B cells[6]. Belimumab is a humanized monoclonal antibody that binds to BAFF and prevents its effects at the BAFF-, BCMA- and TACI receptors. Belimumab is currently FDA approved for the treatment of SLE – a condition with elevated BAFF levels. In MS, elevated levels of BAFF in the CSF have been linked to greater cortical lesion load. Additionally, BAFF levels are elevated in the setting of B cell depletion therapy, and the effects of this elevation on the immunophenotype of reconstituting B cells are unknown5. In a recent study in renal transplantation belimumab, in addition to standard treatment, demonstrated a trend towards a reduction in naïve B cells, a reduction in memory B cells and an increase in the ratio of IL-10 to IL-6 in both memory and transitional B cells[7]. Additionally, blocking BAFF in vitro led to an increase in IL-10 production even from memory B cells[7]. These effects would be expected to be beneficial in MS based on the effects of B cell depletion, as well as other disease-modifying therapies that reduce MS disease activity[8].

A recent trial of tabalumab in RRMS (NCT00882999) that was reported at the 2018 AAN meeting showed no increase in disease activity in the Tabalumab group compared to placebo – based on the primary outcome of Gd-enhancing T1-weighted lesions. Data was posted to clinicaltrial.gov in late 2018 and there appears to no serious safety signal in any of the tabalumab groups, with an apparently lower ARR noted in the tabalumab groups. Also, there was a decrease in the mature naïve B cell number with tabalumab treatment with smaller reductions in the memory B cells. Based on this data, we would hypothesize that

blocking BAFF in MS would be safe unlike the neutralization of APRIL that led to increased disease activity[9].
Patients with MS who receive immunomodulatory and immunosuppressive therapies are at increased risk of infections. As a result, vaccination against pathogens is an important part of the management of patients with MS receiving DMTs. However, immunization response is lower in many patients who receive immunosuppressive therapies. For example, long-term B-cell depletion in patients with rheumatoid arthritis receiving rituximab has been shown to impair vaccination response to non-T-cell dependent antigens[10]. In contrast, belimumab had no detrimental effect on immunization response with non-T-cell dependent antigens in patients with systemic lupus erythematosus[11].

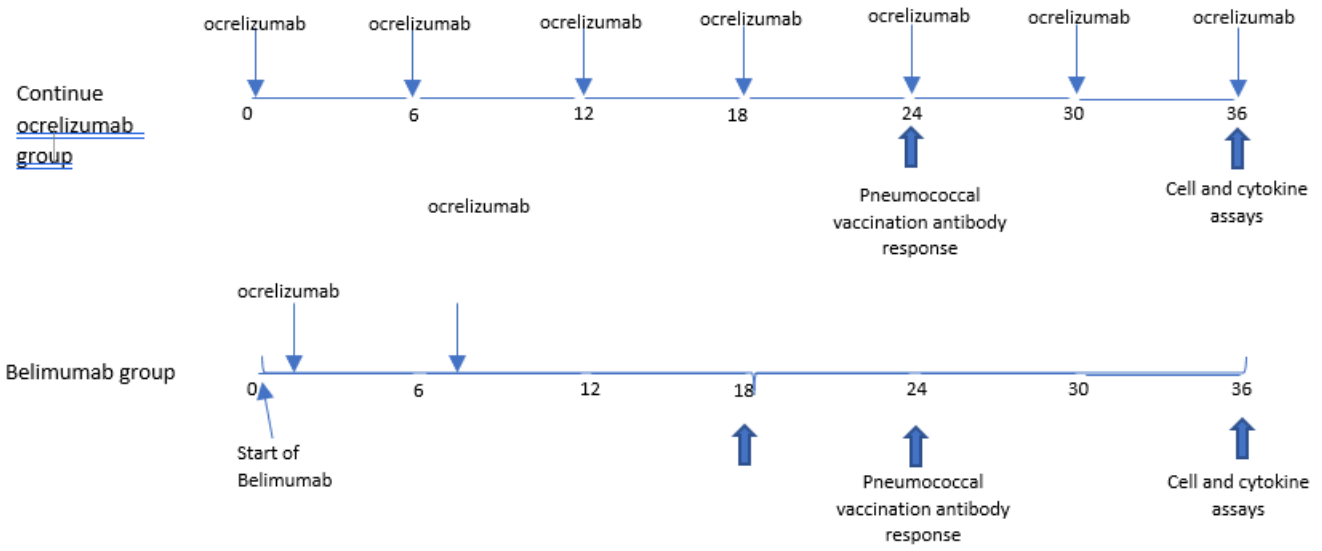
We hypothesize that belimumab, given to patients who received a short course of treatment with B-cell depleting antibody (ocrelizumab), will be safe and equally effective in reducing the MS disease activity (as compared to patients receiving continuous treatment with ocrelizumab); while resulting in less immunosuppression, as measured by antibody response to pneumococcal vaccination. Currently, available treatment strategies in relapsing MS sacrifice the high efficacy for long-term safety or vice versa. The proposed strategy in this application combines the long-term safety and high efficacy of treating patients relapsing MS and can be adopted in a large proportion of patients with this chronic disease.
We propose an open-label experimental medicine trial to assess the safety and activity of adding belimumab to a short course of ocrelizumab in patients with active RRMS.

4. Study Procedures

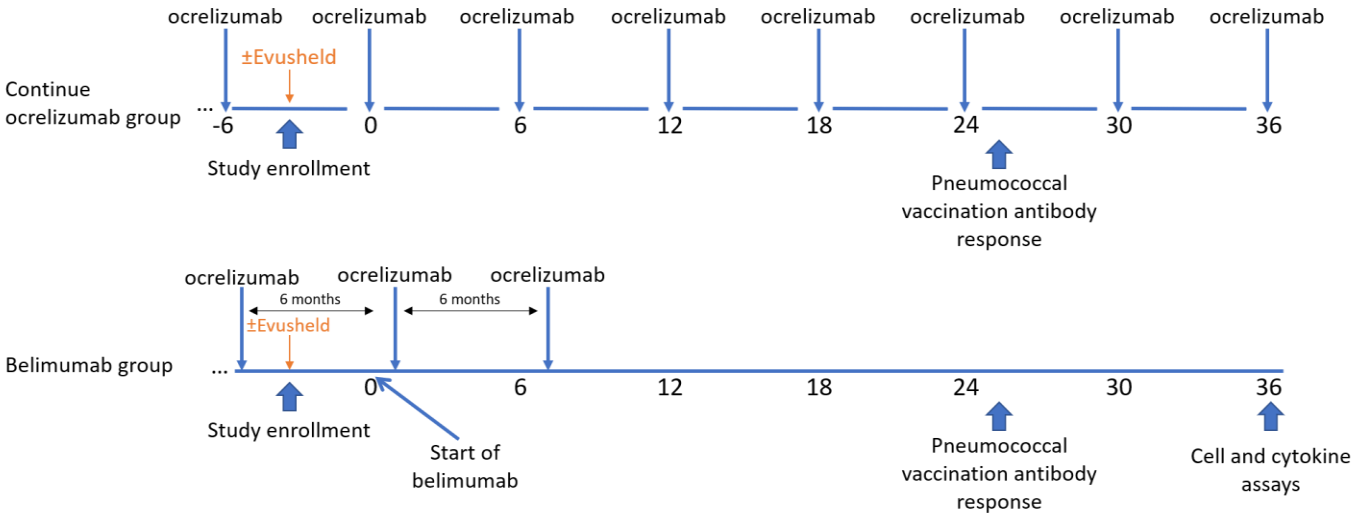
A. Study design, including the sequence and timing of study procedures

This is an open-label, randomized, single center trial. Patients fulfilling the eligibility criteria will be randomized 1:1 to either receiving a form of standard of care, ocrelizumab (300 mg two infusions two weeks apart at baseline and then 600 mg as a single infusion every six months if ocrelizumab-naïve; continued 600 mg infusions every six months if already on ocrelizumab) or belimumab (200 mg SC weekly for 36 months) plus two courses of ocrelizumab (300 mg two infusions two weeks apart at baseline and 600 mg as a single infusion six months later if ocrelizumab-naïve; scheduled next two 600 mg infusions six months apart if already on ocrelizumab). In the group receiving belimumab, belimumab will be initiated four weeks before the first infusion of ocrelizumab or four weeks before the next scheduled ocrelizumab infusion if they are already on ocrelizumab. The belimumab group will only receive two courses of ocrelizumab (three infusions if ocrelizumab-naive), while the continued ocrelizumab group will continue with ocrelizumab infusions every six months throughout the study. If a recruited participant was on an MS disease-modifying treatment other than ocrelizumab, there will be at least 30 days of washout between stopping the disease-modifying treatment and the start of the study medication (either belimumab or ocrelizumab). Given the current COVID19 pandemic, we will recommend one dose of Evusheld (tixagevimab/cilgavimab) – two human monoclonal antibodies against the spike protein of SARS-Cov-2 administered via two separate intramuscular injections – to participants that are already on ocrelizumab and have not received a booster dose or received at least one of the doses while on ocrelizumab, as a prophylaxis against COVID-19 infection.

Timeline of ocrelizumab-naïve participants



Timeline of participants already on ocrelizumab



The evaluation will include a screening visit, then monthly clinic visits for the first six months that will incorporate the use of remote safety visits, then every three months for 36 months. The participants will undergo research brain MRIs with gadolinium-based contrast agent (ProHance®) every six months. The baseline (month 0) time in the belimumab group is the time of the start of belimumab and in the continued ocrelizumab group, the first infusion of the ocrelizumab or the next scheduled ocrelizumab infusion if the participant has been already on ocrelizumab and fulfills the eligibility criteria. So, in the belimumab group, in which belimumab starts one month before the first ocrelizumab infusion or one month before the next scheduled ocrelizumab infusion if the participant has been already on ocrelizumab, the ocrelizumab infusions will happen in the months one and seven.

All ocrelizumab infusions, in both groups, are considered standard of care (and according to the medication label) and will be done as part of routine clinical care.

Schedule of Activities

Schedule of activities in the belimumab group

Visit activity	**Screening**	**Baseline (Month 0)**	**Months 1 and 7 ocrelizumab infusions**	**Safety Visits Month 1, 2, 4, 5**	**Follow-up visits (clinical monitoring) Month 3,9,15,21, 27, 33**	**Follow-up visits (MRI monitoring) Month 6, 12, 18, 24, 30**	**Month 24 and 25 vaccination and antibody assessment**	**End-of-study Month 36**
Informed consent, screening/baseline evaluation	X							
Medical history, relapse assessment	X			X	X	X		X
MRI review	X					X		X
Medication review	X			X	X	X		X
Blinded EDSS	X				X	X		X
MS Functional Composite (MSFC)	X				X	X		
Visit Activity	**Screening**	**Baseline (Month 0)**	**Months 1 and 7 Ocrelizumab infusions**	**Safety Visits Month 1, 2, 4, 5**	**Follow up Visits (clinical monitoring) Month 3, 9, 15, 21, 27, 33**	**Follow up visits (MRI monitoring) Month 6, 12, 18, 24, 30**	**Month 24 and 25 vaccination and antibody assessment**	**End-of-study Month 36**
Symbol Digit Modalities Test	X					X		
Brain MRI	X					X		X
Phlebotomy for serum and PBMC collection	X					X		X
Safety/ Adverse event assessment				X	X	X		X
Safety labs	X (S)			X	X	X		
Start of belimumab injections		X						
Ocrelizumab infusions			**X**					
Pneumococcal vaccination and antibody test							X	

Schedule of activities in the continued ocrelizumab group

Visit activity	**Screening**	**Baseline (month 0)**	**Safety Visits Month 1, 2, 4, 5**	**Follow-up visits (clinical monitoring) Month 3,9,15,21, 27, 33**	**Month 6 ocrelizumab infusion**	**Follow-up visits (MRI monitoring) Month 6, 12, 18, 24, 30**	**Month 24 and 25 vaccination and antibody assessment**	**End-of-study Month 36**
Informed consent, screening/baseline evaluation	X							
Medical history, relapse assessment	X		X	X		X		X
MRI review	X					X		X
Medication review	X		X	X		X		X
Visit Activity	**Screening**	**Baseline (Month 0)**	**Safety Visits Month 1, 2, 4, 5**	**Follow-up visits (clinical monitoring) Month 3, 9, 15, 21, 27, 33**	**Month 6 ocrelizumab infusion**	**Follow-up visits (MRI monitoring) Month 6, 12, 18, 24, 30**	**Month 24 and 25 vaccination and antibody assessment**	**End-of-study Month 36**
Blinded EDSS	X			X		X		X
MS Functional Composite	X			X		X		
Symbol Digit Modalities Test	X					X		
Brain MRI	X					X		X
Phlebotomy for serum and PBMC collection	X					X		X
Safety/ Adverse event assessment			X	X		X		X
Safety labs	**X** (S)		X	X		X		X
Ocrelizumab infusion		**X**			**X**	X		X
Pneumococcal vaccination and antibody test							X	

Labs and assessments include:

1. Vital signs assessed and recorded at screening, at baseline, and each visit immediately before infusion and during infusion.

2. Complete blood count with differential (CBC), at screening, baseline and monthly through the first six months and then every three months.

3. Chemistry at screening, baseline, and monthly through the first six months and then every three months.

4. Pregnancy testing for WCBP and results before each dosing.
   Urine or serum pregnancy testing acceptable
   1. Timing of pregnancy test must be < 7 days before first dose
   2. Pregnancy testing- at each follow-up visit and safety visit
   3. At least four months (5 half-lives) post last dose

5. LFT frequency: at screening, baseline, and monthly through the first six months and then every three months.

6. Serum IgG: at screening, baseline, and at monthly through the first six months and then every three months.

7. HIV and hepatitis B and C serologies and tuberculosis (T-spot or Quntiferon Gold): at screening.

8. Suicidality assessed at screening, baseline and every visit *using the Columbia Suicide Severity Rating Scale (CSSRS http://www.cssrs.columbia.edu/)*

B. Study duration and number of study visits required of research participants

Participants will be in the study for 36 months. The total number of study visits required is 19 – not including any unscheduled visits.

C. Blinding, including the justification for not blinding the trial.

This is an open-label trial. One of the main reasons for this design is practical considerations – since blinding would require placebo infusions every 6 months in one arm in addition to administration of steroids and anti-histaminic medications before these placebo infusions – which are logistically challenging to set up and could potentially expose patients to unnecessary harm.

The other important consideration is that the majority of outcomes are not subjective – vaccine response, imaging, and immunological outcomes and hence would not be significantly affected by the lack of blinding. Additionally, for more subjective outcomes, we will have independent assessing and treating physicians to help avoid bias.

D. Description of what happens to participants receiving therapy when the study ends or if a participant's participation in the study ends prematurely.

At the end of the trial, participants in the continuous ocrelizumab arm will continue treatment with this agent. Participants in the belimumab arm will be transitioned to an alternative disease-modifying therapy by their treating physician based on a discussion of various available options.

If participants are removed or leave the study prematurely from either arm, they will be transitioned to an alternative disease-modifying therapy by their treating physician based on a discussion of risk versus benefit profile of various available options.

E. Definition of treatment failure or participant removal criteria.

Participant participation in the study may be terminated for the following reasons or if the investigator deems it to be in the best interest of the patient.

- Develop of PML or other opportunistic infection (see Risks section below)
- Develop abnormal liver functions as detailed below
- New infection with hepatitis B, hepatitis C, HIV or TB detected on routine safety testing
- Develop breakthrough MS disease activity (see below)
- Hypersensitivity to any of the study agents
- Pregnancy
- Develop suicidal ideation, intent or behavior

- **Liver Chemistry Stopping Criteria**

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

- IP should be discontinued if any of the following criteria are met
  - ALT Absolute: ALT >8xULN
  - ALT Increase:
    - ALT >5xULN but <8xULN persists for >2 weeks
    - ALT >3xULN but <5xULN persists for >4 weeks

- Bilirubin: ALT >3xULN and bilirubin >2xULN (>35% direct bilirubin)

  - Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT >3xULN and bilirubin >2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on the dipstick, indicating direct bilirubin elevations and suggesting liver injury
  - All events of ALT >3xULN and bilirubin >2xULN (>35% direct bilirubin) or ALT >3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
- INR: ALT>3xULN and INR>1.5, if INR measured

- Cannot Monitor:
  - ALT >5xULN but <8xULN and labs cannot be monitored weekly for >2 weeks
  - ALT >3xULN but <5xULN and labs cannot be monitored weekly for >4 weeks

- Symptomatic: ALT >3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

  - New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Required Actions, Monitoring, and Follow up Assessments following ANY Liver Stopping Event

Actions:

- Immediately discontinue study treatment

- Report the event to GSK within 24 hours

- Perform liver event follow up assessments (as stated below)

- Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)

- Do not rechallenge the subject with study treatment.
- In the event that liver stopping criteria are met as a result of DILI, or if there is any reasonable likelihood that the liver event is related to study treatment, IP may not be resumed (i.e., rechallenged).
In the occasional circumstance in which there is a clear underlying cause, other than drug-induced liver injury (DILI) of the liver stopping event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis), with evidence of resolution, and compelling evidence of benefit from belimumab, restart of investigational product (IP) may be considered, but only following consultation with GSK medical affairs Physician or PPL and GSK GCSP Physician. [It should be noted that internal GSK governance processes would be required prior to permitting the resumption of IP]. GSK will communicate the outcome of an internal review to Study Sponsor. Restart is not permitted following liver stopping event when the underlying cause was alcohol-related.

Monitoring:

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs

- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline

- A specialist or hepatology consultation is recommended For All other criteria:
- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs

- Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

Follow Up Assessments:

- Viral hepatitis serology (Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin>2xULN

- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

- Record use of concomitant medications including acetaminophen, herbal remedies, other over the counter medications

- Record alcohol use

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009])

Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease

Increased Monitoring Criteria with Continued Therapy

Criteria

- If ALT >5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks

OR

- ALT >3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks

Required Actions

- Notify GSK within 24 hours of learning of the abnormality to discuss subject safety

- Subject can continue study treatment

- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

- If ALT decreases from ALT 5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

In the event of Treatment Restart (Appendix 2)

- Liver chemistries must be followed at least once weekly following study treatment restart until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.

- If after study treatment restart participant again meets protocol-defined liver chemistry stopping criteria, study treatment must be permanently discontinued.

Additional stopping criteria

Participants in the belimumab arm who experience a relapse (as defined in Section 8 under criteria for initiation of rescue medication) and begin rescue medication (ocrelizumab 600 mg every 6 months) will stop further treatment with belimumab.

5. Inclusion/Exclusion Criteria

Inclusion criteria:

- Diagnosis of RRMS based on McDonald criteria 2017
- Age > 18
- A clinical relapse in the past 12 months OR an enhancing lesion on brain/ spinal cord MRI in the past 6 months OR a new T2/FLAIR/STIR lesion on a brain/spinal cord MRI obtained in the past 6 months (compared to a previous MRI obtained within one year from the latest MRI). This criterion does not apply to the subgroup of people that are already on ocrelizumab.
- Female Subjects: Not pregnant or nursing and at least one of the following conditions apply: a. Non- childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy or postmenopausal defined as 12 months of spontaneous amenorrhea. b. Child-bearing potential and agrees to use one of the contraception methods as described by the investigator or designee, from Day 0 until 24 weeks after the last dose of study medications (See details below).
- Liver function at the time of screening: alanine aminotransferase (ALT) < 2x upper limit of normal (ULN); bilirubin <= 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
- Fully vaccinated against COVID-19 defined as 2 weeks after the second dose in a 2-dose series RNA vaccines (such as the Pfizer or Moderna vaccines) or 2 weeks after a single-dose viral vector vaccine (such as Johnson & Johnson's Janssen vaccine).

Exclusion criteria:

- Prior therapy:
  - Currently on ocrelizumab and the first dose of ocrelizumab was given more than two years before the screening visit) [patients whose last MS DMT was ocrelizumab and the first dose of ocrelizumab was given within two years prior to the screening visit can be eligible for this study]
  - Has ever received any of the following B-cell targeted therapy: rituximab, other anti-CD20 agents besides ocrelizumab, anti-CD22 (epratuzumab), anti-CD52 (alemtuzumab), BLyS-receptor fusion protein (BR3), TACI fragment, crystallizable (Fc), or belimumab
- Prior use of cladribine, mitoxantrone, cyclophosphamide or HSCT
- Lymphopenia: a lymphocyte count <500/ millimeter (mm)^3
- Neutrophils <1.5X10E9/L.
- Drug sensitivity: a history of sensitivity to any of the study medications, or components thereof or a history of drug or other allergies including a previous anaphylactic reaction to parenteral administration contrast agents, human or murine proteins or monoclonal antibodies
- Treatment with steroids in the last 30 days
- Clinically unstable medical or psychiatric disorder

- Have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, poses a significant suicide risk
- Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
- Substance abuse: has evidence of current drug or alcohol abuse or dependence
- 365 Day prior therapy: has received a biologic investigational agent other than B-cell targeted therapy [e.g., abetimus sodium, anti CD40L antibody (e.g., BG9588/ IDEC 131; investigational agent applies to any drug not approved for sale in the country in which it is being used]

- 30 Day prior therapy: has received any of the following within 30 days before Day 0: a) Any other MS disewasew-modifying therapy, not mentioned above (including fumaric acid esters, S1P receptor modulators, teriflunomide, and natalzimaub). Glatiramer acetate and interferons are permitted up to the day of starting the investigational medication . Intravenous, oral, and Inhaled steroids and new topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed.
- 30 Day prior therapy: has received a live virus vaccine or a non-biologic investigational agent.
- Malignancy: has a history of malignancy in the past 5 years except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
- Have a history of a primary immunodeficiency
- Have a significant IgG deficiency (IgG level < 400 mg/dL)
- Have an IgA deficiency (IgA level < 10 mg/dL)
- Infection history:
  - Currently on any suppressive therapy for chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, and atypical mycobacteria)
  - Hospitalization for treatment of infection within 60 days of Day 0.
  - Use of parenteral (IV or IM) antibiotics (anti-bacterial, antiviral, anti-fungal, or anti-parasitic agents) within 60 days of Day 0
- Other disease/conditions: has any of the following: a) clinical evidence of significant unstable or uncontrolled acute or chronic diseases (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, neurological, malignancy or infectious diseases) which, in the opinion of the investigator, could confound the results of the study or put the subject at undue risk; b) a surgical procedure planned in the 6 months after Day 0; c) a known history of any other medical disease (e.g., cardiopulmonary), laboratory abnormality, or condition (e.g., poor venous access) that, in the opinion of the investigator, makes the subject unsuitable for the study
- Hepatitis status:
  - Serologic evidence of current or past Hepatitis B (HB) infection based on the results of testing for HBsAg and HBcAb as follows: Patients positive for HBsAg or HBcAb are excluded
  - A positive test for Hepatitis C antibody
- HIV: known to have a historically positive HIV test or tests positive at screening for HIV.
- Laboratory abnormalities: has an abnormal laboratory assessment, which is judged clinically significant by the investigator.
- Drug Sensitivity: has a history of sensitivity to any of the study medications, or components thereof or a history of drug or other allergies including a previous anaphylactic reaction to parenteral administration contrast agents, human or murine proteins or monoclonal antibodies that, in the opinion of the investigator or Medical Monitor, contraindicates their

participation.
- Any contraindication to undergoing MRI
- TB: tests positive at screening for tuberculosis.
- History of severe allergic reaction after a previous dose of the 23-valent pneumococcal vaccines, and history of a severe allergy to any component of this vaccine.
- Impaired decision making capacity or impaired ability to provide informed consent.

Contraception Requirements

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.
Abstinence
Abstinence from penile-vaginal intercourse must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%
- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

6. Drugs/ Substances/ Devices

Ocrelizumab: Participants, in both groups will receive ocrelizumab, an FDA-approved medication for the treatment of relapsing forms of MS, according to the medication label. One group will stop the infusions after two courses and one group will continue the infusions every six months through the end of the study. Overall, ocrelizumab is administered as an FDA-approved medication according to its label in this study.

Belimumab: The common name of the investigational product is BENLYSTA. The generic United States Adopted Name / International Non-Proprietary Name (USAN/INN) is belimumab; the GlaxoSmithKline (GSK) code for the drug is GSK1550188.

Belimumab drug product for subcutaneous (SC) use will be provided as a liquid formulation in sterile prefilled syringes assembled into two different devices. For the prefilled syringe presentation, belimumab liquid is filled into USP Type I glass syringes with a staked needle (27-gauge thin wall), sealed with a latex-free rubber stopper, and stored at 2 to 8C protected from light. The liquid prefilled syringes are also assembled into two devices: (1) a safety shielding device and (2) an autoinjector device.

Belimumab will be supplied as 1 mL prefilled syringe containing 200 mg liquid belimumab (200 mg/mL). The medication will be administered subcutaneously once a month (starting at baseline). The first subcutaneous injection of belimumab will be under the supervision of a healthcare professional. Subjects will remain under clinical supervision for 3 hours thereafter.

Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as injection-related systemic reactions, and monitor subjects closely. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions. A patient may subsequently self- inject, or a patient caregiver may administer belimumab after the healthcare professional determines that it is appropriate. after the first supervised injection and at the discretion of the investigator, subjects who are adequately trained may self-administer all subsequent doses at home. Comprehensive written instructions on injection technique are required to be provided to the study subject by the investigator. After the first dose, subjects who do not feel adequately trained with self-injection may return to the site for further training. Patients who cannot self-administer the study agent must have a reliable resource (e.g., a caregiver) to administer the subcutaneous injection.

Patients or their caregivers will not administer the study agent until they receive proper training in subcutaneous injection technique.

Subjects will be made aware of the potential risk of delayed-onset acute hypersensitivity, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention in the event of its development.

COVID-19 booster shot: It is possible that during the course of the study, a COVID-19 booster shot will be recommended to the participants due to the immunosuppressive nature of the medications. Several studies have shown that people with MS that take ocrelizumab have an impaired antibody response to COVID-19 vaccines compared to the general population[12,13]. There is not enough information about belimumab and the effectiveness of the vaccines, but based on its immunomodulatory action it may have an impact on it.

7. Study Statistics

Sample size calculations: based on Chatham et al. and Bingham et al. more than 95% of belimumab-treated SLE patients responded to pneumococcal vaccination, while only 55% of patients of rituximab-treated RA patients mounted a response against pneumococcal antigens. Assuming 95% antibody response in the belimumab group and 55% antibody response in the continuous ocrelizumab group, 14 participants in each group will provide 80% power (with an alpha of 0.05) to show a difference between the two groups. We will plan on 20 participants per arm to account for dropouts (anticipated rate is approximately 20%).

Analysis plan for primary, secondary and exploratory outcomes:
No formal statistical hypotheses will be tested in this study. Because the study includes no prospectively defined formal hypothesis testing, no adjustment for multiplicity will be required for the primary and secondary endpoints.

Primary outcome variables
Response to pneumococcal vaccination - One of the primary endpoints of the study is the proportion of patients with positive antibody responses to >=1 of the 23 pneumococcal vaccine serotypes measured four weeks post-vaccination. A positive antibody response is defined as a two-fold increase from pre-vaccination levels against >=1 of the 23 pneumococcal serotypes measured. For patients with unquantifiable pre-vaccination levels, a positive antiboy response is

considered to be a post-vaccination level of >0.6 mg/mL (>2-fold increase above the lower limit of quantification [>0.3 mg/mL] for this assay).

Safety - The other co-primary endpoint is the proportion of participants experiencing an AE/ SAE. We will use chi-square test to compare the proportions between the two groups.

Secondary outcome variables

Disease activity – Measured by Annualized relapse rate (ARR). A clinical relapse is defined as a new or worsening neurologic symptom(s) with an objective change on the EDSS of at least 1.5 points for participants with baseline EDSS scores of 0 and at least 1-point change for participants with EDSS of 1 or more, as determined by the examining neurologist. Symptoms must have been attributable to MS, last ≥48 hours, been present at normal body temperature, and preceded by at least 30 days of clinical stability.

Disability progression – Measured by the change in MSFC scores, EDSS scores and by the proportion of patients in each group that demonstrate a worsening of their EDSS score (sustained for three months).

Radiological disease activity – Measured by the number of new Gd-enhancing lesions on any scan following the baseline or the number of new/ enlarging T2 lesions on any scan as compared to the month-6 MRI brain.

Immunological outcomes – Measured by the proportion of various B cell subsets – naïve. transitional or memory, and the expression of co-stimulatory and antigen presentation related molecules on B cells. For T cells, this would be measured as the proportion of various T cell subsets – naïve, effector, effector memory or central memory and the expression of various cytokines (IFNg, IL-17, and GM-CSF).

The majority of secondary and exploratory analyses will utilize a mixed model for repeated measures approach with fixed categorical effects of treatment, visit, and treatment-by-visit interaction and fixed continuous covariates of baseline values and baseline values-by-visit interaction. An unstructured covariance structure will be used to model the within-patient errors, shared across treatments.

8. Risks

Currently, B-cell depleting agents such as ocrelizumab are utilized in relapsing-remitting MS on a continual basis (every 6 months infusion indefinitely). While this is an effective strategy in terms of reducing inflammatory disease activity (clinical or radiographic), the adverse effects include increased risk for infections (URI, herpes viral infections, reactivation of hepatitis B[14]), hypogammaglobulinemia, reduced efficacy of vaccines and possibly increased malignancy risk[2,15]. This trial will assess the ability of belimumab therapy as an add-on to ocrelizumab to produce a prolonged remission of multiple sclerosis disease activity in the setting of discontinuation of B-cell depletion (to avoid these long-term adverse effects).

Potential Risks:

The major concerns for a strategy of discontinuation of B cell therapy along with belimumab treatment would include the return of inflammatory disease activity or increased immunosuppression-related complications. Risk mitigation strategies are listed below for each of these aspects.

- *Disease activity*

There is a potential for the return of disease activity following cessation of B cell depletion and B cell reconstitution. Hence, we would need to monitor closely for increased/ return of disease activity in both study arms with both clinical and imaging metrics.

- This would occur clinically in trial visits as judged by the treating physician – every three months and at unscheduled visits as needed
- Using MRI to look for the presence of new T2/ T1 Gd-enhancing lesions - every six months during the study.

The overall risk is low given prior data from a phase-2 study using ocrelizumab and intensive monitoring is likely to identify recurrence of inflammatory disease activity and institute rescue therapy to prevent further relapses and progression of the disease. Additionally, given the increased relapse rate noted in the ATAMS trial[9], there is a theoretical risk of worsening of inflammatory disease activity with belimumab. This is mitigated by the additional treatment with ocrelizumab and the recent data from the trial of tabalumab in RRMS which showed no worsening of disease activity at five different doses of tabalumab.

See the criteria for beginning rescue medication below.

- *Complications related to immunosuppression*

We will also closely monitor patients for infectious complications at each study visit or at unscheduled visits as needed.
We will include an infectious diseases expert on the DSMB to assist with decisions regarding the association of any detected infections with belimumab.

- *Suicidality*

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation [Bachen, 2009; Timonen, 2003; Stenager, 1992]. In a recent one-year, randomized, double-blind, placebo-controlled post-marketing study (BEL115467) of 4,003 subjects with SLE (1:1 randomization):

o Serious adverse events (SAE) of suicidal ideation or behavior or self-injury were reported in 0.7% (n= 15) of subjects receiving belimumab intravenously 10mg/kg (IV) vs. 0.2% (n=5) of subjects taking placebo.

o No suicide-related deaths were reported.

o SAEs of depression were reported in 0.3% (n=7) of subjects receiving belimumab 10mg/kg IV vs. <0.1% (n=1) taking placebo.

o On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (n=48) subjects on belimumab 10mg/kg IV reported suicidal ideation or behavior and 2.0% (n=39) subjects on placebo reported suicidal ideation or behavior

For this reason, patients should be clinically assessed for suicidal ideation and/or behavior at each visit.

- *PML*

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

If PML is suspected, this should be immediately reported to GSK. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Rescue Medication and criteria for initiation

Participants that have evidence of clinical or radiological breakthrough as noted below will receive rescue medication – Ocrelizumab 600 mg every 6 months. Additionally, participants will also receive steroids for the treatment of relapses as determined by their treating neurologist.

Criteria for beginning rescue medication (ocrelizumab) include:

1) a confirmed clinical relapse (as defined above)

   or

2) presence of new T2/ Gd-enhancing lesions on an MRI more than six months after beginning the trial.

This will ensure that patients who have a return of disease activity are treated in a timely manner to prevent any worsening of their lesion load. Belimumab treatment will be discontinued if a participant in the belimumab arm requires rescue medication.

Stopping rules for the study:

If more than 4 participants in belimumab plus ocrelizumab arm require re-treatment with ocrelizumab during the follow-up period, we will put the trial on hold until the DSMB can convene and decide whether the trial can continue.

If there is an occurrence of an opportunistic infection that has not previously been linked to B cell depletion in the belimumab arm, this would lead to immediate cessation of the study until reviewed by the DSMB.

Additionally, any deaths that are potentially linked to the use of belimumab will also lead to cessation of the study pending review by the DSMB.

Data safety monitoring board:

The study will also include a data safety monitoring board that will monitor the safety of the study and will meet routinely throughout the conduct of the study and help with decisions regarding whether to continue the trial. This will include – at least one biostatistician, one infectious disease expert and a neurologist with expertise in MS

Standard Adverse Event Information

Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study

- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self- harming intent. This should be reported regardless of sequelae

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that does not worsen

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated

headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT >= 3xULN **and** bilirubin >= 2xULN (>35% direct) (or ALT >=3xULN and INR>1.5 if INR measured) termed 'Hy's Law' events (INR measurement is not required, and the threshold value stated will not apply to patients receiving anticoagulants)

NOTE: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record the presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin >= 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Pregnancy

Any pregnancy that occurs during study participation must be reported to GSK. To ensure subject safety, each pregnancy must be reported within two weeks of learning of its occurrence. The pregnancy must be followed up to determine the outcome (including premature termination) and the status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be reported to GSK within 24 hours.

Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
AEs will be collected from the start of study treatment and until the follow-up contact. SAEs will be collected over the same time period, as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time of consent to participate in the study up to and including any follow-up contact.

Adverse Events of Special Interest:

In addition to the standard safety protocol language, the following adverse events of special interest should be mentioned in the protocol and assessed for frequency in the final report.

- Serious Hypersensitivity or Infusion Reactions
- Serious infections, including herpes zoster and opportunistic infections
- Malignancy
- Suicidal thought, intent or behavior
- Fatal events

Communicating Safety Information:

SAE reporting to GSK should be accomplished via one GSK point of contact, as follows:

- For studies conducted in multiple countries:

- GSK Central Safety Department Global Mailbox: Safety information from studies conducted in multiple countries should be sent via email notification **within 24 hours of awareness** for all unblinded SAEs reported for subjects who received belimumab, regardless of Investigator/designee/Institution causality assessments, to the GSK Central Safety Department: US.NAPS@gsk.com.

  o These SAEs include events reported from open-label studies and from subjects randomized to belimumab in double-blind studies in which the blind was broken (in stream and/or at end of study). .

- In addition, all SAEs arising from the study that remain blinded on the Institution database during the course of the study will be forwarded to GSK retrospectively by Institution using copies of regulatory reports (e.g., CIOMS 1 or MedWatch) and within five working days of Institution database unblinding, where study participants are exposed to belimumab, regardless of Investigator/designee/Institution causality assessments against belimumab.

- For studies conducted in a single country:

- GSK Local Operating Company safety department: In single country studies, report all unblinded SAEs reported for subjects who received belimumab, through the GSK Local Operating Company (LOC) safety department via their local mailbox or central safety at GSK US.NAPS@gsk.com (to be established at the time of contract negotiation). The local mailbox will be provided as appropriate at the time of contract development.

  o These SAEs include events reported from open-label studies and from subjects randomized to belimumab in double-blind studies in which the blind was broken (in stream and/or at end of study). Placebo cases should not be reported).

- In addition, all SAEs arising from the study that remain blinded on the Institution database during the course of the study will be forwarded to GSK retrospectively by Institution using copies of regulatory reports (e.g., CIOMS 1 or MedWatch) and within five working days of Institution database unblinding, where study participants are exposed to belimumab, regardless of Investigator/designee/Institution causality assessments against belimumab.

Regulatory Reporting Requirements for SAEs by Study Sponsor

The study Sponsor is responsible for and undertakes to, assess all clinical safety information arising during the Clinical Trial in order to generate all safety reports as required. Such safety reports will include, but may not be limited to, Individual Case Safety Reports ("ICSRs") for Suspected Unexpected Serious Adverse Reactions ("SUSARs") and, Development Safety Update Report(s) ("DSURs"). The study Sponsor is responsible for submitting such reports to all concerned regulatory authorities in all countries and regions where the Clinical Trial will be conducted, relevant Independent Ethics Committee(s) ("IEC") and individual Clinical Trial investigator(s), as required, within applicable timelines.

9. Benefits

Potential benefits:

The potential benefit of belimumab therapy in the setting of B cell depletion would involve a skewing of the reconstituting B cells to an anti-inflammatory phenotype and potentially a prolonged duration of disease remission following discontinuation of B cell therapy.

Additionally, in the long run, this could result in a reduction in adverse effects related to prolonged immunosuppression that is currently associated with the use of ocrelizumab on an ongoing basis (see above).

Another potential benefit would be the mobilization of B cells from compartments such as the brain and meninges, which could then be targeted more readily by B cell depleting therapy and may result in greater benefit for MS patients. This provides a rationale for beginning Belimumab treatment prior to the first infusion of ocrelizumab.

10. Payment and Remuneration

Participants will be paid US$20 for each study visit for the compensation of travel costs and parking. Participants who finish all the study procedures will receive an additional US$75 at the end of the participation.

11. Costs

The cost of the initial set of labs that may determine the eligibility of patients for receiving ocrelizumab, as well as the cost of ocrelizumab and ocrelizumab infusions (which are all part of the standard of care) will be billed to participants and their insurance. The rest of the study procedures, including clinic visits, belimumab, brain MRIs and labs during the study will be part of the study and will not be billed to the participants and their insurance.

If the patient needs testing or treatment outside of the score of the study; such as more frequent brain MRI, spinal cord MRIs or treatment for relapses, as part of the standard of care, they will also be billed to the participants and their insurance.

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