Belimumab for Maintenance Therapy in Idiopathic Inflammatory Myositis

Protocol

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Amendment 6

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Background :

Idiopathic inflammatory myositis (IIM) is a systemic inflammatory disorder characterized by chronic inflammation involving muscle tissue and could be accompanied by inflammation in the skin and other organs (lungs, heart, intestinal tract) . It typically results in symmetrical, proximal muscle weakness, characteristic skin rash and could cause interstitial lung disease and heart failure. Given some of the similarities between systemic lupus erythematosus (SLE) and IIM, the objective of this study is to explore whether the B Lymphocyte Stimulator (BLyS) pathway plays an important role in the pathogenesis of IIM as it does in SLE. BLyS overexpression in transgenic mice leads to B cell hyperplasia and the development of severe autoimmune disease.[1,2,3] Marked tissue up-regulation of the BAFF transcript was demonstrated in IIM: 14-fold increase in Polymyositis and 12-fold increase in Dermatomyositis compared with normal muscle[4]. Circulating BLyS levels were shown to be elevated in the sera of patients with myositis. Moreover, independent correlations were observed between serum BLyS levels and: 1) markers of myositis disease activity, 2) the presence of interstitial lung disease, and 3) CRP and CPK blood levels.[5] The highest BLyS serum concentrations were found in dermatomyositis and in those patients who were anti-Jo-1 positive.[6] Studies have shown that treatment with corticosteroids induced a marked decrease in BLyS concentrations in patients with SLE[7]and in IIM[8,9]. Similar data showing decreased BLyS expression is available for other immunosuppressives[8], suggesting that not only steroids, but other immunosuppressive therapies, affect the BLyS pathway in patients with IIM. These observations suggest that BLyS may be an important therapeutic target in IIM.

We propose a multicentre double-blind, placebo-controlled trial to evaluate the efficacy and safety of belimumab as a maintenance therapy in adults with refractory IIM.

Target Patient Population:

Adults with refractory IIM will be enrolled. IIM is defined as Dermatomyositis (DM) or Polymyositis (PM), meeting the Bohan & Peter (1975) diagnostic criteria for definite or probable DM or PM. Refractory IIM is defined as chronic active IIM with a history of inadequate response or intolerance to three months of glucocorticoids and/or at least a history of inadequate response or intolerance to three months of one other immunosuppressive agent (IS) (azathioprine, methotrexate, mycophenolate mofetil, leflunomide, tacrolimus, cyclosporine, cyclophosphamide, Rituximab or intravenous gamma globulin [IVIG]).

Study Objectives:

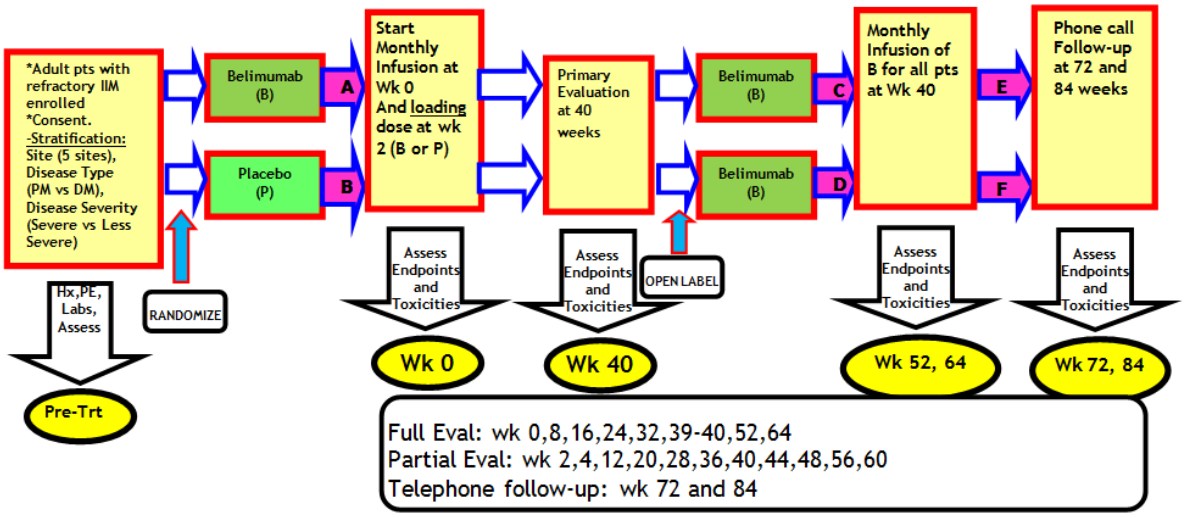
a. To compare the clinical response rates in refractory IIM patients on stable background treatment receiving monthly intravenous (IV) belimumab to patients receiving placebo.
b. To assess the safety of monthly IV belimumab in patients with IIM.
c. To evaluate the steroid-sparing effect of monthly IV belimumab added to background treatment of IIM.
d. To evaluate the biologic effects of belimumab treatment on various B cell populations and inflammatory cytokine levels.

Study Design:

This is a multicenter randomized double-blind placebo controlled trial to evaluate the efficacy and safety of Belimumab as a maintenance therapy in adults with refractory idiopathic inflammatory myositis (IIM).

The Northwell Health Department of Rheumatology will be the coordinating site for this multi-center clinical trial. We plan to enroll 30 patients into the trial. Enrollment is competitive. Study enrollment will be carried out for two years and each patient will be followed for a total of 84 weeks.

Figure 1. Study Flowchart-overview (please check Study Schedule, Appendix A for details).



At point A, a loading dose of Belimumab will be given at week 2.
At point B, a loading dose of Placebo (saline) will be given at week 2.

a. Study Procedures and Schedule:

A simplified flowchart of the study procedure is given in Figure 1.

After consent, a patient will be randomized to either Belimumab+ standard of care (B) or Placebo+ standard of care (P). Randomization will be according to the two important stratification variables, namely, disease type (Polymyositis vs. Dermatomyositis) and disease severity (severe vs less severe) and will occur at week 0 (first infusion). There will be two major study phases: the randomized phase of the study and the open-label phase of the study, described below.

Screening: Once the patient signs the consent form, a screening period of up totwo weeks will initiate to determine the patient's eligibility for the study, prior to entering the randomization phase. Only eligible patients will enter the randomization phase.

Randomized Phase: Monthly infusions (of either B or P) will start at week 0 and continue every four weeks until week 36 (10 months) for the "randomized" phase of the study. In addition, there will be a "loading dose" at week 2 (per drug [IND] specifications). The loading dose will consist of either Belimumab or Placebo (saline) in the B or P treatment arms, respectively.

Open Label Phase: Monthly infusions (of B) will start at week 40 and continue every four weeks until week 64 (6 months) for the "open-label" phase of the study.

A comprehensive evaluation of the patient (Physical exam and history, vital signs, AEs, CBC and metabolic panel, GGT, myoglobin, pregnancy test, urinalysis, ESR, CRP, CPK, immunoglobulins, muscle and health evaluations, physician global assessment, patient self-assessments, serum level sampling) will be conducted at weeks 0, 8, 16, 24, 32, 39-40, 52, 64. A less comprehensive set of evaluations (vital signs, AEs, CBC and metabolic panel, GGT, pregnancy test) will be conducted at weeks 2, 4, 12, 20, 28, 36, 40, 44, 48, 56, 60. A detailed schedule of visits and procedures is outlined in appendix A.

A telephone follow-up conversation will also be conducted at weeks 72 and 84.

Optional Exploratory Studies

Blood based biomarker assessments and blood based RNA assessments will be performed on stored samples for consenting patients at Northwell Health only. See Appendix A (schedule of events).

b. Randomization:

The Biostatistics Unit at the Feinstein Institute for Medical Research [BU-FIMR] will develop a web based randomization plan for the study. A randomization schema will be generated by the BU-FIMR for each participating site using the method of permuted blocks. Subjects will be randomly assigned in a 1:1 ratio to either Belimumab or Placebo, according to two stratification variables, namely, disease type (Polymyositis or Dermatomyositis) and disease severity (severe or less severe). The Biostatistics Randomization Management System (BRMS) is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using their personal computer. The BRMS allows for multi-center, stratified, and single/double blinded RCTs, using permuted blocks. Randomization notifications are automatically sent to the PI and other authorized personnel. Using BRMS is a good way to maintain compliance in RCTs.

c. Stratification:

Randomization will be according to the two important stratification variables: disease type (Polymyositis vs. Dermatomyositis) and disease severity (severe vs less severe) and will occur at week 0 (first infusion). The number of immunosuppressive agents used by the patient over the last year (corticosteroids are not included) will be used as a surrogate of disease activity: one or less IS agent over last year versus more than 1 IS agent over last year.

d. Blinding:

This is a double-blind study; both the investigator and the patient will be blinded to the treatment assignment in the randomized phase of the trial. At the end of the 40 week randomized treatment phase all subjects will start the 20 week open label phase and therefore the drug will be dispensed in the unblinded fashion.

For each study site, there will be a designated unblinded research coordinator (URC) and a blinded research coordinator (BRC). The URC will be responsible for obtaining randomization assignments from the BU-FIMR and will oversee the preparation of infusions prior to drug administration. The BRC will be responsible for coordinating patient visits and administration or the infusion (infusion will be masked and not identifiable through any physical characteristics such as color or consistency, as the drug is of a powder form mixed in saline solution).

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study (person responsible for receiving and dispensing study agent). Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

If a medical emergency occurs and a decision regarding the subject's condition requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Whenever possible, the investigator should consult with the principal investigator of the study and data safety monitoring board prior to unblinding any subject. Any broken blind will be clearly justified and explained. The lead site and sponsor must be notified of any broken blind regardless of whether it was done for emergency or non-emergency reasons.

e. Concurrent Medications:

Corticosteroids: Patients that are on glucocorticoids at the time of screening will be required to be on a stable background dose for at least 2 weeks prior to screening (prednisone (or equivalent) dose $\leq$ 15 mg daily).

The prednisone dose will remain stable until week 24 of the study, at which time a taper will be allowed at the discretion of the site investigator and principal investigator.

An increase in the dose of oral prednisone will be permitted, if clinically necessary, during the first 8 weeks after randomization without accounting it as a disease flare. In this case, the dose of prednisone must be tapered (to less than or equal to 25% of the baseline dose) by week 12. However, if the dose of prednisone cannot be tapered by week 12, the event will be considered as disease flare at that time.

Any increase of the prednisone dose after week 8 for IIM disease activity or the use of pulse steroids at any time during the study will be considered a disease flare. An increase of the prednisone dose at any time during the study for an event other than worsening of IIM disease activity will require the patient to return to the baseline dose of prednisone within 10 days, without accounting the event as a disease flare. Patients that are considered treatment failures will be allowed to remain in the study, in respective groups, at the discretion of the treating physician and PI.

Immunosuppressive agents (IS): Enrolled patients could have had a history of treatment with any of the following IS agents: azathioprine, methotrexate, mycophenolate mofetil, leflunomide,

tacrolimus, cyclosporine, cyclophosphamide, Rituximab, or intravenous gamma globulin [IVIG]. Patients are not required to be on an IS agent at the time of enrollment.

During the enrollment and study period, **the only allowed IS agents are**: azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, cyclosporine or intravenous gamma globulin [IVIG].

Patients that are on background immunosuppressive (IS) therapy at the time of screening will be required to be on a stable IS agent for ≥ 2 months prior to screening(≥3 months for IVIG), and on a stable dose of IS agent for ≥ 2 weeks prior to screening (except IVIG; no dose change allowed). Dose reduction due to poor tolerance of IS agent will be allowed on a case by case basis.

Therapeutic Agent	**Treatment Duration** prior to Screening ≥	**Dose Increase** prior to Screening ≥
Azathioprine	2 months	2 weeks
Methotrexate	2 months	2 weeks
Mycophenolate mofetil	2 months	2 weeks
Tacrolimus	2 months	2 weeks
Cyclosporine	2 months	2 weeks
IVIG	3 months	none

If a dose increase in IS agent or initiation of a new IS agent is clinically necessary during the randomization phase, this will be considered as a disease flare. The patient will be allowed to continue in their respective assigned group at the discretion of the treating physician and PI.

f. Medications and Therapies Prohibited for Concomitant Use:

a. Anti-B-cell therapy:

i. Wash out of 5 therapeutic half-lives after prior B-cell therapy, or until pharmacodynamic effect would be minimal (e.g., 1 year following Rituximab)

- IgG levels should be measured monthly in this situation
- Benlysta should be discontinued in subjects with IgG levels <250 mg/dL associated with a severe or serious infection

ii. If Rituximab use was medically indicated after the patient's enrolment to the clinical trial, the patient will no longer receive the investigational drug, but enhanced safety monitoring will be required.

b. Intravenous Cyclophosphamide

i. 180 Days Prior to Belimumab

- IgG levels should be measured monthly in this situation
- Benlysta should be discontinued in subjects with IgG levels <250 mg/dL associated with a severe or serious infection

ii. If cyclophosphamide use was medically indicated after the patient's enrolment to the clinical trial, the patient will no longer receive the investigational drug, but enhanced safety monitoring will be required.

c. A live vaccine. (Live vaccines should not be given within 30 days prior to administration or concurrently with belimumab)

d. Any Biologic Investigational Agent (e.g., abetimus sodium, anti CD40L antibody, BG9588/ IDEC 131) or any other investigational agent not approved for sale in the country in which it is being used

i. 365 days Prior to Belimumab:

e. Any Non-Biologic Investigational Agent (investigational agent applies to any drug not approved for sale in the country in which it is being use)

i. 30 Days Prior to Belimumab (or 5 half-lives, whichever is greater)

g. Packaging, Labeling, Preparation and Storage:

Belimumab will be supplied in a 20mL vial containing 400mg of belimumab. Belimumab should be stored at 2-8°C. After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C, or at room temperature. The 400 mg single use vial of study agent will be reconstituted with 4.8 mL SWFI, to yield a final concentration of 80 mg/mL of belimumab.

The study agent label will contain, at a minimum, the following information:

- Product name;
- Concentration;
- Lot number;
- Storage conditions;
- Investigational drug statement; and
- Manufacturer's name and address.

The calculated dose of study agent to be administered to the subject is determined in milligrams (mg) by the assigned treatment group and the subject's body weight in kilograms (kg). The reconstituted study agent will be diluted in 250 mL normal saline for intravenous infusion. An amount of normal saline, equal to the calculated amount of product to be added, should be removed from the infusion bag prior to adding the product. After adding the reconstituted product, gently invert the bag to mix the solution. Subjects receiving placebo will receive 250mL of normal saline for intravenous infusion.

h. Data Management:

The Biostatistics Unit (BU), within The Feinstein Institute for Medical Research (FIMR), provides state-of-the-art statistical and data management support to the research investigators at Northwell Health, as well as other medical research institutions in the New York area. Its staff of ten PhD and Masters level statisticians and two senior applications programmers has extensive experience in the design, data management, and analysis of hundreds of clinical research

projects, including over 250 clinical trials. Primary expertise is in clinical trials, diagnostic testing and screening, the development of predictive models for prognosis, and development of protocols and grant applications.

Definitions:

All patients are required to meet the Bohan & Peter (1975) diagnostic criteria for definite or probable DM or PM (see Appendix B) and be positive for at least one autoantibody (ANA ≥1:80 or RNP or SSA/SSB or any of the myositis specific autoantibody). Patients with the diagnosis of definite or probable PM will require the presence of at least one myositis specific auto-antibody (antisynthetase autoantibodies (anti-Jo-1, PL-7, PL-12, EJ, OJ), anti-SRP, anti-Mi-2, anti-p140[also known as anti-MDA5], anti-p155/140 [also known as anti-TIF], anti-NXP-2 [also known as MJ]). Patients with the diagnosis of definite or probable PM in the absence of myositis specific auto-antibodies will require review of the muscle biopsy results and adjudication of the diagnosis by a committee of 3 experts that will be predetermined in advance.

Refractory Myositis: Refractory myositis is defined as chronic IIM with an inadequate response or intolerance to at least three months of corticosteroids and/or an inadequate response or intolerance to at least three months of at least one other immunosuppressive agent (azathioprine, methotrexate, mycophenolate mofetil, leflunomide, cyclophosphamide, tacrolimus, cyclosporine or IVIG).

Core Set Measures (CSM): All enrolled subjects will be required to have active disease based on the clinical core set measures, which is a standard instrument for assessing myositis disease activity. Active disease using the CSM is defined by International Myositis Assessment and Clinical Studies Group [11]:

1. Manual muscle testing (MMT-8) with a score ≤ 125/150
2. Elevation of at least one muscle enzyme (creatinine kinase [CK]; myoglobin; alanine aminotransferase [ALT]; or aspartate aminotransferase [AST]) to a minimum level of 1.3 times the upper limit of normal.
3. Physician Global Assessment ≥ 2.0 cm using a visual analogue scale (VAS) 10.0 cm in length.
4. Patient Global Assessment ≥ 2.0 cm using a visual analogue scale (VAS) 10.0 cm in length.
5. Global extra muscular disease activity score ≥ 1.0 cm using a visual analogue scale (VAS) 10.0 cm in length. This score is based on the investigator's composite assessment of disease activity of the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac scales on the Myositis Disease Activity Assessment Tool (MDAAT).
6. HAQ disability index with a minimum value of 0.25.

The patient will be required to meet an MMT 8 score of ≤125/150 as a major CSM criterion and at least 2 other CSM criteria to classify as an active disease.

In addition, for patients with ≥ 7 years of IIM, muscle biopsy or muscle MRI within 4 months prior to enrollment will be required to document active myositis to avoid enrolling patients with

significant index of damage/ muscle atrophy. This is not applicable to DM patients with a cutaneous VAS score of >3 cm on a 10 cm VAS scale (MDAAT).

Response rate: The response rate will be assessed by the percentage of patients meeting the definition of improvement (DOI). DOI is based on the definition of improvement developed by the International Myositis Assessment and Clinical Studies Group utilizing 6 core set measures.

DOI: DOI is defined as ≥ 20% improvement in any 3 of the CSM, with no more than 2 CSM worsening by ≥ 25% (excluding MMT)[11].

Definition of Worsening (DOW): Determination of worsening of the disease activity will based on the definition of worsening (DOW) criteria developed by the International Myositis Assessment and Clinical Studies Group (IMACS) utilizing 6 core set measures[11]:

1. worsening of Manual Muscle testing by ≥20% and or Physician Global worsening of ≥ 2cm on a 10 cm VAS or
2. Global extra muscular organ disease activity worsening by ≥ 2cm on a 10 cm VAS on MDDAT, or
3. 3 of 6 CSM worse by ≥ 30%

Disease Flare: IIM Disease Flare is recorded when the patient:

1. reaches DOW;
2. new start or dose increase of corticosteroid or immunosuppressive agent for treatment of IIM after study week 8;
3. an increased dose of corticosteroid before study week 8 and did not return to <25% above the baseline dose by week 12.

Endpoints:

1. **Primary Endpoint:**
   a. Response rate at 40 weeks defined as percentage of patients meeting definition of improvement (DOI) in IIM patients treated with belimumab and standard therapy compared to the percentage of patients meeting DOI treated with placebo and standard therapy.

2. **Secondary Endpoints:**
   a) Incidence of flares: flare rates during 40 weeks randomization period in patients with IIM treated with belimumab and patients treated with placebo and at week 64 in each group.
   b) Time to achieve initial improvement defined as the time to reaching DOI.
   c) Duration of improvement; quantified as the time from achieving improvement to the time of worsening or a disease flare. (Time from 1st DOI to 1st DOW or disease flare event). This will be based on the subset of subjects who achieve improvement.
   d) Percent change in muscle enzyme levels (CPK and myoglobin) from baseline to week 40 and 64 in each respective group
      1. <20% reduction: no response
      2. 20-70% reduction: partial response
      3. >70% reduction: complete response
   e) Percent change in manual muscle assessment (MMT-8) from baseline to week 40 and week 64 in each respective group.

1. <20% reduction: no response
2. 20-70% reduction: partial response
3. >70% reduction: complete response

f) Percent change in prednisone dose from baseline to week 40 and week 64 in each respective group
g) Proportion of subjects, among those on steroids at baseline, able to reduce the prednisone dose to ≤ 5 mg daily at week 40 and week 64 in each respective group.
h) Flare rate in placebo group during the 40 week randomized treatment phase as compared to that group in the 20 week open label phase.
i) Serious adverse event and adverse event rates
j) Changes in B cell populations from baseline to week 40 and week 64
k) Changes in autoantibody titers from baseline to week 40 and week 64
l) Changes in immunoglobulin concentrations from baseline to week 40 and week 64

Inclusion Criteria:

Subjects enrolled in the study must meet the following inclusion criteria:

1) Adults ≥18 years of age
2) Have a diagnosis of:
    a. definite or probable dermatomyositis (DM) by modified Bohan & Peter criteria or
    b. Definite or probable diagnosis of polymyositis (PM) with presence of one of myositis specific antibodies. In the absence of myositis specific auto-antibodies, the diagnosis of PM will require review of the muscle biopsy and adjudication by the predetermined committee of experts.
3) Presence of positive autoantibody (ANA ≥1:80 or RNP or SSA/SSB or any of the myositis specific autoantibody anti-synthetase autoantibodies (anti-Jo-1, PL-7, PL-12, EJ, OJ), anti-SRP, anti-Mi-2, anti-p140 also known as anti-MDA5], anti-p155/140 [also known as anti-TIF], anti-NXP-2 [also known as MJ]).).
4) Have refractory IIM as defined by inadequate response or intolerance to at least 3 months of glucocorticoids and/or an inadequate response or intolerance to at least 3 months at least one other immunosuppressive agent, such as azathioprine, methotrexate, IVIG, mycophenolate mofetil, leflunomide, tacrolimus, cyclosporine cyclophosphamide, and Rituximab.
5) Have active IIM at screening. This requires at least 3 criteria from the CSM (listed above) to be met for enrollment.
6) Dermatomyositis patients that do not meet the MMT criteria, must have:
    a. a cutaneous VAS score of >3 cm on a 10 cm VAS scale (MDAAT) will be required:
    b. elevation of at least one muscle enzyme (creatine kinase [CK]; myoglobin; alanine aminotransferase [ALT]; or aspartate aminotransferase [AST]) to a minimum level of 1.3 times the upper limit of normal,
    c. and 1 additional core set measure
7) For patients with ≥ 7 years of IIM, muscle biopsy or muscle MRI within 4 months prior to enrollment will be required to document active myositis to avoid enrolling patients with significant index of damage/ muscle atrophy. This is not applicable to DM patients with a cutaneous VAS score of >3 cm on a 10 cm VAS scale (MDAAT).
8) Have a stable background glucocorticoid therapy for at least 2 weeks prior to screening

(Prednisone (or equivalent) dose ≤ 15 mg daily)

9) Immunosuppressive therapy (IS) at the time of enrollment is not required. However, a patient receiving IS therapy at the time of enrollment must be on a stable regimen (azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine for ≥ 2 months prior to screening. Patients on intravenous gamma globulin (IVIG) have to be on a stable dose and frequency regimen for ≥ 3 months.

Therapeutic Agent	Treatment Duration prior to Screening ≥	Dose Increase prior to Screening ≥
Azathioprine	2 months	2 weeks
Methotrexate	2 months	2 weeks
Mycophenolate mofetil	2 months	2 weeks
Tacrolimus	2 months	2 weeks
Cyclosporine	2 months	2 weeks
IVIG	3 months	none

10) Have the ability to understand the requirements of the study and provide written informed consent (including consent for the use and disclosure of research-related health information) and comply with the study protocol procedures (including required study visits)

11) Female subjects of childbearing potential must have a negative urine pregnancy test at screening and agree to 1 of the following:
    a. Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent (Sexual inactivity by abstinence 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);
    or
    b. Consistent and correct use of 2 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent
        1) Oral contraceptive, either combined or progestogen alone
        2) Injectable progestogen
        3) Implants of levonorgestrel or etonogestrel
        4) Estrogenic vaginal ring
        5) Percutaneous contraceptive patches
        6) Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
        7) Male partner sterilisation (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. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.

8) Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from the study:

1. Have severe muscle damage as defined by a Muscle Damage Index (MDI) > 5.0 cm using a visual analogue scale (VAS) 10.0 cm in length
2. History of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell).
3. Have a history of a primary immunodeficiency
4. Have a significant IgG deficiency (IgG level < 400 mg/dl) Have an IgA deficiency (IgA level < 10 mg/dL)
5. Discontinuation IS agent < 3 months prior to Screening. Including: azathioprine, methotrexate, mycophenolate mofetil, leflunomide, tacrolimus, cyclosporine, or intravenous gamma globulin [IVIG]
6. Have received Rituximab within 365 days prior to Screening.
7. Have received cyclophosphamide within 180 days prior to Screening
8. Have received treatment with:
    a. Initiated IVIG less than 3 months prior to Screening
    b. Pulse steroids 2 months prior to Screening
9. Have received treatment with Belimumab at any time prior to Screening
10. Have received a biologic investigational agent within 365 days prior to Screening.
11. Have received a non-biologic investigational agent within 30 days or 5 half-lives of the agent (whichever is longer) prior to Screening.
12. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
13. Infection history:
    a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis – including latent tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    NOTE: Testing for latent TB is a standard of care for patients on immunosuppressive therapy and results will be obtained from their medical record. If no TB history is found for these patients, a Quantiferon Gold or PPD test will be performed prior to Day 0 as part of standard of care.
    b. Hospitalization for treatment of infection within 60 days of Day 0.
    c. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 0.
14. Have a historically positive HIV test or test positive at screening for HIV.
15. Have a history of autoimmune hepatitis
16. Hepatitis status will be obtained from patients' medical records. If unavailable, testing will be done as part of standard of care. Patients are excluded if there is evidence of chronic or active Hepatitis B infection with:
    a. Hepatitis B:

i. Presence of positive Hep B surface antigen independent of history of previous exposure to IVIG.
ii. Positive hepatitis B core antibody for patients with no exposure to IVIG
iii. Patients who previously received IVIG and have positive core antibody (Hepatitis B coreAb) and negative Hep B surface antibodies with or without the presence of positive HBVDNA by PCR

- Note: Patients who previously received IVIG and with Hep B core IgG pos and Hep B sAB pos. are allowed to be enrolled but additional safety monitoring procedures must be followed on these patients – please see Appendix C: Follow Up Assessments. The table below describes which types of patients would be eligible based on different Hep B core/surface ab positivity.

Hep Bs ag	+	-/ +	-/ +	–	–	–
Hep B s ab	-/ +	+	-/ +	–	–	+
Hep B core ab IgM	-/ +	+	-/ +	–	–	–
Hep B core ab IgG	-/ +	-/ +	-/ +	+	+ **repeat** –	+
Hep B by PCR	-/ +	-/ +	+	–	–	–
STATUS:	**Not eligible**	**Not eligible**	**Not eligible**	**Not eligible**	**Eligible**	**Eligible**

b. Hepatitis C:
c. Positive hepatitis C antibody with confirmatory hepatitis C viral load by PCR.

17. Clinically significant elevation of GGT (>1.5xULN), bilirubin (>1.25xULN, direct 35%), or INR (>1.2, excluding patients on anti-coagulant therapies) or other clinically significant abnormal laboratory value in the opinion of the investigator.
18. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.
19. Have evidence of serious suicide risk including any history of suicidal behaviour in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, pose a significant suicide risk.
20. Have any concurrent significant medical or psychiatric illness that the investigator considers would make the candidate unsuitable for the study.

Study Drug Administration:

1. **The study agent will be administered by 10mg/kg dose** at 2 weeks intervals for the first 3 doses and every 4 weeks thereafter. It is administered IV over a minimum of 1 hour. During the study visit at each dosing the patient will be monitored and routine laboratory testing will be performed according to standard of care. See Appendix A for infusion dosing schedule.

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

3. **Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions**. In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Infusion reactions occurred more frequently on the first two infusion days and tended to decrease with subsequent infusions. Delay in the onset of acute hypersensitivity reactions has been observed and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed. Therefore, patients should be monitored during and for an appropriate period of time after administration of belimumab. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to the study sites' guidelines or standard operating procedure for IV infusions.

4. **Subjects should be made aware of the signs and symptoms** of delayed-type, non-acute hypersensitivity reactions that have been observed. These include symptoms such as rash, nausea, fatigue, myalgia, headache, and facial edema. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

Safety Considerations and Adverse Events:

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

Adverse Event (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 a 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.

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 do 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

Common adverse events seen in the belimumab lupus trials include; nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, pain in the extremities, depression, migraine and pharyngitis

Serious Adverse Event (SAE): A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

   NOTE: Any death that occurs during study participation must be reported within 24 hours to the lead site and study sponsor. The investigator must identify etiology, relationship to study drug and an SAE case report form must be completed.

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 out-patient 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. **NOTE:** 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 liver injury defined as ALT ≥ 3x ULN **and elevated GGT** ≥ 3x ULN (without elevated CPK, and/or myoglobin)
h. All events of possible drug-induced liver injury with **hyperbilirubinaemia** defined as ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **and** bilirubin ≥ 2xULN (>35% direct)
i. All events of possible liver injury with **increased INR** defined as ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **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 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. **(See Appendix C).**

NOTE:

ULN (Upper Limit of Normal) as determined by the reference range of the local lab

All liver toxicities must be reported to the Sponsor (Northwell Health) and GSK.

Subjects that meet liver stopping criteria (See Appendix C) MUST be reported to GSK within 24 hours.

In the case of a LIVER STOPPING EVENT, follow up assessments should be completed (see Appendix C).

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.

> **NOTE:** 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.

Adverse Events of Special Interest: The following AEs should be monitored closely and reported to the study sponsor immediately.

1. **Serious hypersensitivity reaction or Infusion Reactions** (See Section: Study Drug Administration and Considerations)
2. **Suicidality**: Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation [Bachen, 2009; Timonen, 2003; Stenager, 1992]. For this reason in studies of patients with autoimmune disease, patients should be clinically assessed for suicidal ideation and/or behavior at each visit. If destructive tendencies are suspected, the subject should be referred to a psychologist or other appropriate specialist for evaluation.
3. **Malignancy**
4. **Serious infections**, including herpes zoster and opportunistic infections
5. **Progressive multifocal leukoencephalopathy (PML)**. 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, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. **If PML is suspected, this should be immediately reported to the Medical Monitor.** The appropriateness of continuing study agent, while the case is being assessed, should be discussed.
6. **Abnormal liver enzymes (See Appendix C).** While previous studies of belimumab in lupus have shown no causal relationship between the drug and liver toxicity, liver function will be monitored in all subjects throughout the study (See Appendix C).

Pregnancy:

Any pregnancy that occurs during study participation must be reported using clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported within 2 weeks of learning of its occurrence to the lead site and sponsor. The pregnancy must be followed up to

determine outcome (including premature termination) and 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. Pregnancy testing will occur at every study visits and at 16 weeks after the last treatment dose.

NOTE: Any SAE occurring in association with a 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 promptly reported to the lead site as well as GSK.

Adverse Event and Serious Adverse Event Reporting:

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

- All AEs must be reported to the coordinating site.
- All SAEs must be reported to the coordinating site and local IRB within 24 hours. The coordinating site will report all SAEs to the coordinating site's IRB, the sponsor and the FDA.

All AEs and SAEs must be reported on an Adverse Event/Serious Adverse Event case report form. The study investigator is responsible for noting the relationship of the event to the study drug, the severity of the drug (criteria for grading toxicity will be based on NCI's Common Terminology Criteria for Adverse Events version 4.03), the actions taken with the investigational product, and any other medications used to treat the adverse event or serious adverse event.

Time Period and Frequency of Detecting AEs and SAEs:

The investigator or site staffs are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of the study treatment until the end of the study. SAEs will be collected from the start of the study treatment until the end of the study. All SAEs will be reported to the coordinating site, sponsor and IRB within 24 hours.

NOTE: 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 a subject consents to participate in the study up to and including any follow up contact.

Study Procedures & Assessments:

The following assessments will occur throughout the study (see Appendix A for schedule of events):

- Informed Consent and Inclusion/Exclusion Criteria will be assessed at the screening visit. After a subject signs the informed consent they will enter the screening period (≤ 2 weeks) and have eligibility determined prior to Day 0.
  Laboratory assessments:
  a. CBC, Comprehensive metabolic, GGT, ESR, CRP, CPK, serum myoglobin, immunoglobulins, urinalysis and urine pregnancy test will be collected at screening.
  b. CBC, Comprehensive metabolic, GGT, ESR, CRP, CPK, serum myoglobin, immunoglobulins and urinalysis **collected within 2 weeks prior to screening can be used** for eligibility determination.

c. Testing for latent TB is a standard of care for patients on immunosuppressive therapy and results will be obtained **from their medical record**. If no TB history is found for these patients, a Quantiferon Gold or PPD test will be performed prior to Day 0 as part of **standard of care**.
d. Hepatitis status will be obtained from patients' **medical records**. If unavailable, testing will be done as part of **standard of care** during the screening period.

- Vital signs will be assessed prior to infusion and after the infusion at every visit.
- Adverse events assessed at every visit. Criteria for grading toxicity will be based on NCI's Common Terminology Criteria for Adverse Events version 4.03. (Adverse Events/Serious Adverse Events (CTCAE Version 4.03)
- A Physical Exam will be performed by the Investigator at Screening, Day 0, Week 8, 16, 24, 32, 40, 52, & 64.
- Urine Pregnancy testing for WOCBP will be conducted at each study visit and 16 weeks after last dose. Urine pregnancy tests must be completed < 7 days prior to the first dose and prior to each IP administration, but not more than once a month. In the event that the urine pregnancy test is indeterminate, a serum pregnancy test will be done.
- Laboratory tests: CBC, Comprehensive metabolic, GGT, ESR, CRP, CPK, myoglobin and urinalysis will be collected at every study visit and follow up week 64.
- An immunoglobulin panel will be collected and assessed at: Screening, Week 40, & 64. Under special circumstances monthly IgG monitoring may be required (see Section: Study Design, part f) and will be performed as part of standard of care.
- Flow Cytometry and RNA-seq are collected at: Day 0, Week 8, 40, Week 48, & Week 60 or 64.
- Cytokine levels (and optional research Northwell only) will be measured at: Day 0, Week 40, & Week 60 or Week 64.
- Patients should be clinically assessed for suicidal ideation and/or behaviour at each study visit using the Columbia Suicide Severity Scale (C-SSRS)
- The Investigator will complete a Physician Global Assessment (PGA, a VAS scale of 10cm), Manual Muscle Test-8 (MMT-8), & Myositis Disease Activity Assessment Tool (MDAAT) at Screening, Day 0, Week 8, 16, 24, 32, 40, 52, & 64
- The Investigator will complete a Muscle Damage Index (MDI) assessment at Screening, Week 40 and Week 64
- Health Assessment Questionnaire (HAQ) and Patient Global Assessment (PGA, a VAS scale of 10cm) will be completed by subjects at Screening, Day 0, Week 8, 16, 24, 32, 40, 52, & 64
- Post study follow up phone call with subject conducted at Week 72 and 84.
- Patients who previously received IVIG and with Hep B core IgG positive and Hep B sAB positive will undergo surveillance with Liver function test, Hepatitis Panel and Viral Load every 3 months.

Data Safety Monitoring Plan:

The principal investigator and two independent physicians, designated by the Principal Investigator, will be responsible for the oversight of the data safety monitoring plan. The committee will meet every 6 months to evaluate the rate of unanticipated adverse events. If any

safety signals are identified, recommendations to changes in the protocol or consent will be defined by the committee. Benefit-to-risk assessment will be made in order to determine if the study should continue. The results of these regular meetings will be recorded and disseminated to all participating clinical sites.

Feinstein Biostatistics Unit BUDDY System: Data Management

The Biostatistics Unit (BU), within The Feinstein Institute for Medical Research (FIMR), provides state-of-the-art statistical and data management support to the research investigators at Northwell Health as well as other medical research institutions in the New York area. Its staff of ten PhD and Masters level statisticians and two senior applications programmers has extensive experience in the design, data management, and analysis of hundreds of clinical research projects, including over 250 clinical trials. Primary expertise is in clinical trials, diagnostic testing and screening, the development of predictive models for prognosis, and development of protocols and grant applications.

The Biostatistics Unit provides data management support through its "BUDDY" system ("Biostatistics Unit Database Designed for You"). BUDDY is a highly customized, secure, HIPAA-compliant, web-based database application. It is particularly suited to studies with longitudinal and relational data structures, especially clinical trials. The cost of database development may vary depending upon features requested by the user, including, but not limited to: case report form development, number of unique data screens, transfer of data between another system and BUDDY, data validation checks between screens, image file storage, special queries or reports, translation of adverse event descriptions into MedDRA, and data submission tracking.

The Biostatistics Randomization Management System (BRMS) is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using their personal computer. The BRMS allows for multi-center, stratified, and single/double blinded RCTs, using permuted blocks. Randomization notifications are automatically sent to the PI and other authorized personnel. Using BRMS is a good way to maintain compliance in RCTs.

Statistical Considerations

SPECIFIC STATISTICAL AIMS

The primary objective of the study is to compare subjects in the Belimumab group and subjects in the placebo group with respect to response (improvement) at week 40.

The specific aims of the study are to compare the two treatment arms (Belimumab vs. Placebo [P vs. B]), during the 40-week randomized phase of the study, with respect to the following:

1. Response at week 40.
2. Flare rates during the 40-week treatment period.
3. Time-to-achieve (initial) improvement during the 40-week randomized phase of the study
4. Duration of improvement during the 40-week randomized phase of the study, among those who achieved improvement (this is essentially a time-to-flare/relapse analysis from the time that you achieved improvement)
5. Change in muscle enzyme levels (CPK, myoglobin) from baseline to week 40
6. Change in MMT-8 from baseline to week 40
7. Change in prednisone dose from baseline to week 40

8. Proportion of subjects able to reduce prednisone dose to ≤5 mg at week 40
9. Change in B cell populations, immunoglobulin levels and BLys levels from baseline to week 40.
10. Change in autoantibody titers from baseline to week 40.
11. Rates of SAEs and AEs experienced

STATISTICAL METHODS

All subjects will be analyzed according to the intention-to-treat [ITT] principle. A subject will be considered evaluable and will be included in the intention-to-treat analysis if he/she received at least the first five of the planned infusions during the randomized phase of the study. Subjects who do not get the first five infusions will be considered 'drop-outs'. It should be noted that the study protocol calls for patients remaining on their treatment assignment. However, adjustments in dosages of medications used in their 'standard care' are permitted during the first 8 weeks. Analyses that take into account the actual treatment received (e.g. accounting for compliance, etc.) will be carried out as a secondary analysis (per protocol [PP] analysis).

1. For specific aim 1, the two treatment arms [B vs. P] will be compared with respect to the proportion of subjects who respond to treatment at 40 weeks (improvement according to definition), using either a chi-square test or Fisher's exact test, as appropriate.

2. For specific aim 2, either a chi-square test or Fisher's exact test, as appropriate, will be conducted to compare the proportion of subjects who had any flares during the 40-week randomized phase. For this analysis, each subject will be categorized at the end of 40 weeks as having had one or more flares or not having had any flares. In addition, we can also examine the total number of days that a subject had a specific flare during the course of the 40-week treatment, and compare the two treatment arms using the 'Incidence density ratio' method.

3. For specific aim 3, standard methods for survival analysis will be carried out. The Kaplan-Meier (KM) product limit method will be used to estimate overall "time-to-achieve (initial) response/improvement". Ninety-five percent confidence intervals will be calculated using Greenwood's formula for computing the standard error. Subjects who have not achieved improvement as of week 40 will be considered 'censored' for the event (event=improvement/response).

4. For specific aim 4, similar methods as indicated for specific aim 3 will be conducted. The analysis for this aim will be limited to the subset of subjects in each treatment arm who show improvement at anytime during the randomized phase of the trial. A subject who has not flared/worsened/relapsed as of week 40 will be considered 'censored' for the event (event=flare/relapse).

5. For specific aims 5, 6, 7, 9 and 10, each of the outcome variables of interest (uncensored continuous or categorical) will be analyzed separately, using a mixed model approach to repeated measures analysis of variance (MMRMANOVA) with the main effects of treatment arm (B vs. P), Disease type (PM vs DM), Disease Severity (Severe vs. Less Severe) and time (baseline vs. 40 weeks). If feasible, statistical interactions between

treatment and time (baseline vs. week 40; or all available data at each study visit) or other factors of interest will be examined (e.g. Treatment X Disease Type; Treatment X Disease Severity). The treatment-by-time interaction term, will demonstrate whether the trajectories (or patterns of change) in the outcomes of interest are different between treatment groups. Data transformations may be used, in order to meet the necessary assumptions for the mixed models analyses. If transformations do not achieve the assumptions needed, a rank transformation or an appropriate non-parametric method will be considered.

If the analysis using a mixed model approach is not feasible due to the pattern of the data, then, a simplified analysis comparing the two treatment arms with respect to percent change (reductions) in muscle enzymes, MMT-8 and prednisone dose will be carried out using either a t-test or the Mann-Whitney test, as appropriate. A chi-square test or Fisher's exact test, as appropriate, may also be used if the continuous measures are grouped according to pre-specified categories (e.g. reduction in CPK will be categorized as No Response, Partial Response or Complete Response according to whether the percent reduction was <20% vs. 20%-70% vs. >70%, respectively).

6. For specific aim 8, the proportion of subjects who were able to reduce their daily prednisone dose to ≤5 mg at week 40, will be compared using either a chi-square test or Fisher's exact test, as appropriate.

7. For specific aim 11, either a chi-square test or Fisher's exact test, as appropriate, will be conducted to compare the proportion of subjects who experienced any SAEs or AEs during the randomized phase of the study. For this analysis, each subject will be categorized at the end of 40 weeks as having had any SAEs/AEs or not having any SAEs/AEs.

Multivariable analyses (logistic, cox) will be conducted for the above outcomes, if feasible. However, this may be limited by the sample size.

SAFETY DATA

There will be no formal interim analyses or formal statistical stopping rules. However, statistical summaries of adverse event rates using 95% exact confidence intervals will be provided to the data safety monitoring board as need. During regular bi-annual meetings the data safety monitoring board will evaluate the overall rate of adverse events and unanticipated problems. Upon review the group will determine whether there are any changes needed to the anticipated benefit-to-risk assessment and if the study should continue. The results of these regular meetings will be recorded and disseminated to the other participating clinical sites. Safety data will be collected in the form of adverse events (AEs), serious AEs (SAEs) and laboratory parameters (e.g., hematology, chemistry, etc.). AEs will be recorded with the date of onset, severity, relationship to study drug, and disposition. AEs will be translated into a standard classification system such as COSTART or MedDRA. AE data will be summarized according to incidence rates, by treatment arm and by whether or not the AE was treatment related. AEs will be summarized using descriptive statistics and tabulated according to treatment group for each strata. The AE report will be descriptive, rather than inferential.

SAMPLE SIZE CONSIDERATIONS

We plan to enroll 30 evaluable patients with 15 in each of two treatment arms [B vs. P].

From available trials in IIM, there is an observed placebo effect of 0%-40% at 12 weeks[9,10] and 0% at 52 weeks[9]. These results demonstrate that the placebo response rate at 40 weeks can be very variable. One clinical study looking at rituximab in myositis was the first prospective, double-blind, randomized trial in myositis and the largest clinical trial ever performed in the inflammatory myopathies[16]. This trial employed a unique design; subjects were divided into two groups: early-start and delayed-start of rituximab. Overall, 83% of enrolled subjects (with severe refractory disease) met the DOI by the end of the trial, despite lack of statistical significance between groups. An alternate double-blind, placebo-controlled trial of etanercept (50 mg subcutaneously weekly for 52 weeks) where 16 subjects were randomized showed that: all 5 subjects receiving placebo were treatment failures (median time to treatment failure: 148 days)[17]. In contrast, 5 of 11 subjects in the etanercept arm were successfully weaned off prednisone; the median time to treatment failure in this group was 358 days ($p = 0.0002$). This data shows that for myositis trials, placebo response is often close to 0%. In order to achieve a clinically meaningful difference between study treatment arms, the response rate of the treatment group would need to be at least50%.

We hypothesize (optimistically) the response rate at 40 weeks in the placebo arm to be 5%. We further assume that a magnitude of difference of 45% would be clinically meaningful (this corresponds to a 50% response rate in the Belimumab arm.

Based on the assumption that a difference of 45% in response rates at 40 weeks between Placebo and the investigational agent, Belimumab, would be clinically meaningful, then, a two group chi-square test (alpha=0.05, two sided test) will yield 80% power to detect a difference between the Placebo arm week 40 response rate of 5% and a Belimumab-treated arm week 40 response rate of 50% (Odds ratio=19) when the sample size in each group is 15, assuming the dropout rate is 0%.

Table 1 below shows the sample size requirements for various pairs of (hypothesized) 40-week response rates and assumptions on what would be a clinically meaningful difference between treatment arms. Corresponding sample sizes are provided for the specified range of parameters. Calculations were based on a two-sided chi-square test to achieve 80% power (alpha=0.05).

Table 1. Sample Size Requirements (N) for Various Effect Sizes (80% power, two-sided chi-square test, alpha=0.05), attrition rate =0%.

Index	PLACEBO RESPONSE	BELIMUMAB RESPONSE	Difference	ODDS RATIO	REQUIRED N PER GROUP	TOTAL N, (assuming no
1	15%	60%	45%	8.5	17	17
2	15%	55%	40%	6.9	22	44

Index	PLACEBO RESPONSE	BELIMUMAB RESPONSE	Difference	ODDS RATIO	REQUIRED N PER GROUP	TOTAL N, (assuming no
3	10%	60%	50%	13.5	14	28
4	10%	55%	45%	11	16	32
5	5%	60%	55%	28.5	11	22
6	5%	55%	50%	23	12	24
7	5%	50%	45%	19	15	30

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Appendix A. Study Schedule

	SCREENING PHASE	RANDOMIZED TREATMENT PHASE											OPEN LABEL TREATMENT PHASE							Post Treatment Follow Up			
	Screening	Day 0	Week 2*	Week 4*	Week 8	Week 12*	Week 16	Week 20*	Week 24	Week 28*	Week 32	Week 36*	Week 40	Week 40	Week 44*	Week 48*	Week 52	Week 56*	Week 60*	Week 64	Week 72	Week 76	Week 84
Clinical /Physical																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X																						
Physical Exam and History	X	X			X		X		X		X		X				X			X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Assess AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
MMT	X	X			X		X		X		X		X				X			X			
MDAAT	X	X			X		X		X		X		X				X			X			
Physician Global Assessment	X	X			X		X		X		X		X				X			X			
MDI	X												X							X			
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
HAQ (completed by subject)	X	X			X		X		X		X		X				X			X			
Patient Global Assessment (completed by subject)	X	X			X		X		X		X		X				X			X			
Post Study Follow Up Phone Call w/Subject																					X		X
Study Agent Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Laboratory																							
CBC w/differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Comprehensive Metabolic Panel (AST, ALT, ALP incl.)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
GGT Liver Enzyme	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ESR	X	X			X		X		X		X		X				X			X			
CRP	X	X			X		X		X		X		X				X			X			
CPK total	X	X			X		X		X		X		X				X			X			
Serum Myoglobin	X	X			X		X		X		X		X				X			X			
Urinalysis w/Microscopy	X	X			X		X		X		X		X				X			X			
Immunoglobulins (IgG, IgA, IgM)	X												X							X			
Pregnancy test (WOCBP)[§]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Flow Cytometry		X ǂ			X ǂ								X ǂ			X ǂ			X ǂ	X ǂ			
RNA-Seq		X ǂ			X ǂ								X ǂ			X ǂ			X ǂ	X ǂ			
Cytokine Levels		X¤											X¤						X¤	X¤			
Optional Research Sampling (Northwell Only)		X£			X£								X£			X£			X£	X£			

* Note: Patients will be monitored, assessed and have routine blood tests performed according to standard of care at each infusion visit

§ Note: Pregnancy testing will occur at each outlined study visit and at 16 weeks after the last treatment dose

ǂ Note: Blood samples should be collected at the following time points: Day 0, Week 8, 40, Week 48, Week 60 or 64

¤ Note: Blood samples should be collected at the following time points: Day 0, 40, Week 60 or 64

£ Note: Optional Blood samples should be collected at the following time points: Day 0, Week 8, Week 40, Week 48, Week 60 or Week 64

Appendix B. Bohan & Peter (1975) Diagnostic Criteria for Polymyositis and Dermatomyositis[12]

Diagnostic Criteria for Polymyositis and Dermatomyositis (Bohan & Peter)

1. Symmetric proximal muscle weakness determined by physical examination.

2. Elevation of serum skeletal muscle enzymes (particularly creatine kinase and aldolase), serum glutamate| oxaloacetate, pyruvate transaminases, and lactate dehydrogenase.

3. The electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges.

4. Muscle biopsy specimen abnormalities of degeneration, regeneration, necrosis, phagocytosis, and interstitial mononuclear infiltrate.

5. Typical skin rash of dermatomyositis, including a heliotrope rash, Gottron sign, and Gottron papules.

Using these criteria, polymyositis is defined as definite (all of criteria 1-4), probable (any three of criteria 1-4), or possible (any two of criteria 1-4). Dermatomyositis is defined as definite (5 plus any three of criteria 1-4), probable (5 plus any two of criteria 1-4), or possible (5 plus any one of criteria 1-4).

Appendix C.: Liver Chemistry Stopping and Follow Up Criteria

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). These criteria have been amended for this myositis protocol to accommodate for a specific population of myositis patients with ALT/AST abnormalities as a result of muscle injury. Baseline bilirubin, GGT and INR must be at or near normal. (Note: ULN – upper limit of normal as determined by the reference range of the local lab. All liver toxicities must be reported to the Sponsor (Northwell Health). Subjects that meet liver stopping criteria MUST be reported to GSK within 24 hours.)

- ALT Absolute:
    - ALT ≥ 8xULN (without elevated CPK, and/or myoglobin)
    - If ALT ≥ 8xULN **and serum GGT** ≥ 3xULN (irrespective of CPK and/or myoglobin values)
- ALT Increase:
    - ALT ≥ 5xULN but <8xULN (without elevated CPK, and/or myoglobin) **and GGT ≥3xULN,** persists for ≥2 weeks
    - ALT ≥ 3xULN but <5xULN (without elevated CPK, and/or myoglobin) **and GGT ≥3xULN,** persists for ≥4 weeks
- Bilirubin: ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) [a, b]
- INR: ALT ≥ 3xULN and INR>1.5, if INR measured [b]
- Cannot Monitor:
    - ALT ≥ 5xULN but <8xULN (without elevated CPK, and/or myoglobin) **and GGT ≥3xULN** and labs cannot be monitored weekly for ≥2 weeks
    - ALT ≥ 3xULN but <5xULN (without elevated CPK, and/or myoglobin) **and GGT ≥3xULN** and labs cannot be monitored weekly for ≥4 weeks
- Symptomatic: ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **and GGT ≥3xULN** associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity [c]

a) 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 bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

b) All events of ALT ≥ 3xULN(without elevated CPK, and/or myoglobin) **and GGT ≥3xULN**

c) All events of ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **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
d) 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 and Follow up Assessments following ANY Liver Stopping Event

Actions:

- Immediately discontinue study treatment
- Report the event to GSK within 24 hours
- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE
    - All events of ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **and elevated GGT ≥3xULN or**
    - All events of ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or**
    - All events of ALT ≥ 3xULN (without elevated CPK, and/or myoglobin) **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)
- Perform liver event follow up assessments
- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see MONITORING below)
- Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted

MONITORING:

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, GGT, 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, GGT, 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)

For subjects who have had IVIG in the past and with Hep B core IgG pos and Hep B sAB pos. additional safety monitoring procedures must be followed. HBVDNA testing must be done every 2 months and when ALT or AST elevations increase > 2.5xULN during the study

-
- Blood sample for pharmacokinetic (PK) analysis, obtained within [insert time interval recommended by clinical pharmacokinetics representative] after last dose (PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM. Not required for single-dose studies
- Serum GGT, 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 on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications
- Record alcohol use on the liver event alcohol intake case report form

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]). NOTE: not required in China

- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

Increased monitoring criteria with continued therapy

Criteria

- For subjects who have had IVIG in the past, additional HBVDNA testing must be completed when ALT or AST elevations increase to >2.5xULN during the study
- If ALT ≥5xULN and <8xULN (without elevated CPK, and/or myoglobin) 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 (without elevated CPK, and/or myoglobin) and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks
- If ALT ≥5xULN and <8xULN (without elevated CPK, and/or myoglobin) and **GGT is ≥** 1.5xULN to < 3xULN 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 (without elevated CPK, and/or myoglobin) and **GGT is ≥** 1.5xULN to < 3xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks

Required Actions

- Notify the Sponsor (Northwell Health) and 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, GGT, 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 ≥ 5x ULN and <8xULN to ≥3xULN but <5xULN (without elevated CPK, and/or myoglobin) and **GGT is ≥** 1.5xULN to < 3xULN, continue to monitor liver chemistries weekly.
- If, after 4 weeks of monitoring, ALT <3xULN (without elevated CPK, and/or myoglobin) **and** bilirubin <2xULN **and/or** GGT is <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

NOTE: If any of above rules are met, but the investigator feels that laboratory changes are due to myositis activity and not liver injury, the investigator will discuss with the Sponsor (Northwell Health) and GSK to determine the continuation of the subject in the protocol.