

## TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Protocol Amendment

<b>Title:</b>	A randomized, double blind (sponsor open), comparative, multi-center study to evaluate the safety and efficacy of subcutaneous belimumab (GSK1550188) and intravenous rituximab co-administration in subjects with primary Sjögren's syndrome.
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**Compound Number:** GSK1550188

**Development Phase:** II

**Effective Date:** 25-JUN-2019

**Protocol Amendment Number:** 6

## Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1 for Sweden
Protocol amended in response to comments received from Swedish regulatory authority.		
Local 2014N220285_02	2015-NOV-20	Amendment No. 2 for Norway
Protocol amended in response to comments received from Norwegian regulatory authority.		
Local 2014N220285_03	2016-JAN-04	Amendment No. 3 for Italy
Protocol amended in response to comments received from Italian regulatory authority.		
Global 2014N220285_04	2016-JUN-13	Amendment No. 4
<p>The primary reason for this amendment is to modify the subject selection criteria (specifically exclusion criterion #30 pertaining to exclusionary laboratory thresholds) to better align with the intended population characteristics.</p> <p>Other amendments include the following:</p> <ul style="list-style-type: none"> <li>• Greater clarity is provided regarding the committees involved in monitoring subject safety and review of study data as well as the governance of the study.</li> <li>• It has been made clear that a single formal interim analysis is planned.</li> <li>• The subject withdrawal and study stopping criteria have been modified.</li> <li>• Greater detail is provided regarding prohibited and permitted medications.</li> <li>• Additional guidance is provided regarding vaccination.</li> <li>• Guidance has been provided for tuberculosis assessment during the screening period.</li> <li>• The pregnancy section has been modified to clarify the duration of follow up required.</li> </ul>		

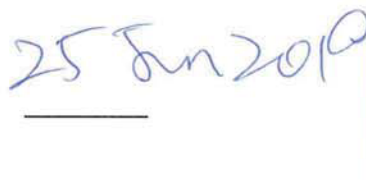
GlaxoSmithKline Document Number	Date	Version
<p>This amendment incorporates country-specific changes required by Regulatory Authorities during prior review. In addition, changes have been made throughout to provide clarity for the conduct of the study and correct typographical errors.</p> <p>All changes made in Amendment 4 are summarized, rationalized and detailed in Appendix 13 (Section 12.13).</p>		
Global 2014N220285_05	2018-MAY-11	Amendment No. 5
<p>The primary reason for this amendment is to clarify the definition of “sponsor open” in Section 6.3, with respect to study blinding. Additional minor clarifications have been made throughout the protocol.</p>		
Global 2014N220285_06	2019-JUN-25	Amendment No. 6
<p>The primary reason for this amendment is to clarify the timing of unblinding for GSK staff and site staff. Additional minor updates have been made in several sections of the protocol.</p>		

## SPONSOR SIGNATORY

PPD



25 Jun 2019



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Date

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): EudraCT number 2015-000400-26

**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number 201842

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature	Date	



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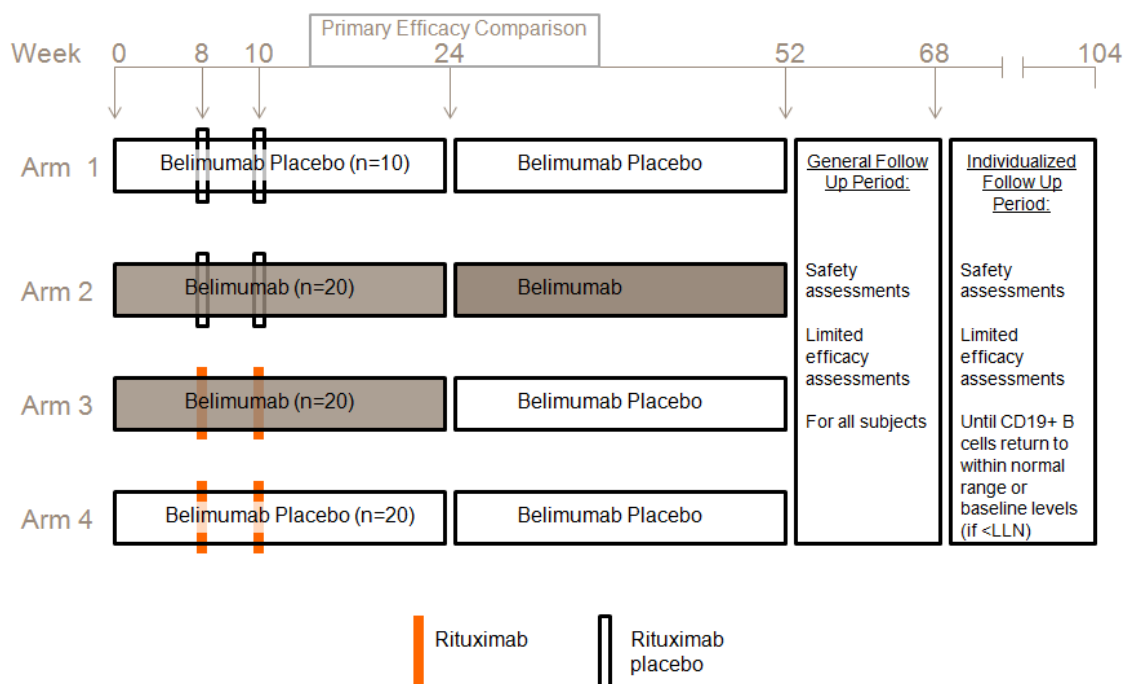
# 1. PROTOCOL SYNOPSIS FOR STUDY 201842

## Rationale

Primary Sjögren's syndrome (pSS) is a common autoimmune disease characterized by oral and ocular dryness as well as systemic manifestations. B cells are thought to play a central pathogenic role. There are no disease modifying treatments for this disease and existing approved therapies consist of symptomatic treatments that do not address the autoimmune pathology. Therefore, substantial unmet medical need exists for a disease modifying therapy; one that can stop B-cell mediated autoimmune damage, alleviate glandular as well as constitutional symptoms, and ameliorate extra-glandular target organ manifestations.

Clinical studies suggest that targeting B-cells with belimumab or rituximab may improve disease symptoms of patients with Sjögren's syndrome. In addition, scientific evidence suggests that dual B-cell targeted immunotherapy with both B lymphocyte stimulator (BLyS) blockade (i.e., belimumab) and B cell depletion (i.e., rituximab; anti-CD20) may be more efficacious than targeting either mechanism alone. Therefore, this proof of mechanism study will assess whether either dual B-cell immunotherapy (i.e., co-administration of belimumab and rituximab) or belimumab monotherapy demonstrates a favorable safety and tolerability profile and results in improvements in clinical status, functional outcomes and mechanistic endpoints in comparison to placebo or rituximab monotherapy.

## Overall Design



The primary efficacy comparison for this study at Week 24 will be between the co-administration therapy arm and the placebo arm. Once approximately 35 subjects have

completed week 24, a formal interim analysis will be performed on the available data. Following this interim analysis, a number of actions could be taken: the study could continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation up to a maximum of 120 total subjects in the study.

### Key Objective(s)/Endpoint(s)

Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"> <li>Safety and tolerability of anti-BLyS / anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies</li> </ul>	<ul style="list-style-type: none"> <li>Safety and tolerability; including incidence of SAEs and AESIs</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>Clinical efficacy of anti-BLyS / anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies</li> <li>Assessment of anti-BLyS / anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies on tissue B-cells</li> </ul>	<ul style="list-style-type: none"> <li>ESSDAI score over time</li> <li>Stimulated salivary flow over time</li> <li>Oral dryness numeric response scale over time</li> <li>B cell quantification within salivary gland biopsy at Week 24</li> </ul>
<b>Exploratory</b>	
<ul style="list-style-type: none"> <li>Assessment of mechanism and durability of effect of anti-BLyS/anti-CD 20 co-administration therapy and anti-BLyS and anti-CD20 monotherapies</li> </ul>	<ul style="list-style-type: none"> <li>Sustained efficacy of anti-BLyS/anti-CD 20 co-administration at Week 52</li> <li>Extended mechanistic assessment of anti-BLyS/anti-CD20 co-administration and monotherapies in blood, tissue and saliva at Week 24 and 52</li> </ul>

### Treatment Arms and Duration

Approximately 70 subjects will be recruited into the study initially. At Day 0, subjects will be randomized 1:2:2:2 to one of the four treatment arms below.

1. Placebo Arm: Approximately 10 subjects will receive belimumab placebo weekly subcutaneous injections to Week 52 and rituximab placebo infusions at Weeks 8 and 10.

2. Belimumab Monotherapy Arm: Approximately 20 subjects will receive 200 mg weekly subcutaneous injections of belimumab to Week 52 and placebo rituximab infusions at Weeks 8 and 10.
3. Co-administration Therapy Arm: Approximately 20 subjects will receive belimumab 200 mg weekly subcutaneous injections for 24 weeks followed by weekly placebo belimumab injections to Week 52 with rituximab 1,000 mg intravenously at Weeks 8 and 10.
4. Rituximab Monotherapy Arm: Approximately 20 subjects will receive 1,000 mg IV rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of placebo belimumab to Week 52.

### **General Follow up Period**

Subjects in all arms will receive investigational product (IP) until Week 52 (completion of the treatment phase). All subjects will enter a 16-week general follow-up period after the Week 52 visit or after discontinuation, if a subject discontinues IP and withdraws from the treatment phase visits prior to Week 52.

### **Individualized Follow up Period**

After completing the general follow-up period, subjects with CD19+ B-cell levels below the lower limit of normal (LLN) (or less than 90% of baseline, if baseline value was below LLN) will enter an individualized safety follow-up phase and return to the clinic for visits every 12 weeks up to a maximum of two years (i.e., up to Week 104).

### **Type and Number of Subjects**

Adult subjects with symptomatic and systemically active disease as well as evidence of glandular reserve function will be recruited. Initially, approximately 70 subjects will be randomized. Withdrawn subjects may be replaced, and there is potential to further increase the number of subjects in one or more arms following sample size re-estimation, up to a maximum of 120 recruited into the study. The randomization ratio will vary dependent on the number of treatment arms continuing following the interim analysis

### **Analysis**

**Hypotheses and Treatment Comparisons:** The primary objective of the study is to investigate the safety and tolerability of the co-administration of belimumab with rituximab and of belimumab monotherapy. No formal statistical comparisons will be conducted to assess this objective. If deemed appropriate, to investigate the secondary efficacy and mechanistic endpoints, the following comparisons may be conducted:

- Co-administration belimumab/rituximab treatment arm vs. Placebo arm
- Co-administration belimumab/rituximab treatment arm vs. Rituximab monotherapy arm

- Co-administration belimumab/rituximab treatment arm vs. Belimumab monotherapy arm
- Belimumab monotherapy arm vs. Placebo arm
- Belimumab monotherapy arm vs. Rituximab monotherapy arm

If deemed appropriate, these exploratory comparisons will be made investigating ESSDAI score, stimulated salivary flow, oral dryness numeric response scale and a subset of salivary gland histology assessments and B cell quantification. For all other parameters, no formal statistical comparisons will be made, although trends over time will be investigated across all treatment arms.

**Sample Size Calculations:** Initially approximately 70 subjects will be recruited into the study. The study is not powered to detect pre-defined differences.

**Interim Analysis:** Once half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy analysis may be conducted. to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be taken: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study

**Data Analysis Considerations:** All data will be descriptively summarized, graphically presented and listed appropriately. The relationship between the mechanistic endpoints (e.g., salivary gland B cell quantification) and clinical effects (e.g., ESSDAI score) will be graphically presented. The consistency in the changes over time between the endpoints will be assessed and further exploratory analyses to characterize relationships between endpoints may be conducted. Comparisons between treatment groups will be conducted if deemed appropriate. For example, the change from baseline in ESSDAI score will be statistically analyzed using a mixed effect model repeated measurement (MMRM) analysis comparing the co-administration with placebo at each time point. Similar analyses may be conducted for other secondary endpoints. In addition, based on the data that we observe in the study, probabilities of success may be determined, for example, what is the probability that we would observe a certain change in ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

## **2. INTRODUCTION**

### **2.1. Study Rationale**

Primary Sjögren's syndrome (pSS) is a common autoimmune disease characterized by oral and ocular dryness as well as systemic manifestations. B cells are thought to play a central pathogenic role. There are no disease modifying treatments for this disease and existing approved therapies consist of symptomatic treatments that do not address the autoimmune pathology. Therefore, substantial unmet medical need exists for a disease modifying therapy; one that can stop B-cell mediated autoimmune damage, alleviate glandular as well as constitutional symptoms and ameliorate extra-glandular target organ manifestations.

Clinical studies suggest that targeting B-cells with belimumab or rituximab may improve disease symptoms of patients with Sjögren's syndrome. In addition, scientific evidence suggests that dual B-cell targeted immunotherapy with both B lymphocyte stimulator (BLyS) blockade (i.e., belimumab) and B cell depletion (i.e., rituximab) may be more efficacious than targeting either mechanism alone. Therefore, this proof of mechanism study will assess whether either dual B-cell immunotherapy (i.e., co-administration of belimumab and rituximab) or belimumab monotherapy demonstrates a favorable safety and tolerability profile and results in improvements in clinical status, functional outcomes and mechanistic endpoints in comparison to placebo or rituximab monotherapy.

### **2.2. Brief Background**

Sjögren's syndrome is manifest by sicca symptoms, constitutional findings, and potentially severe, life-threatening organ-specific extra-glandular manifestations. It is characterized by a combination of features including oral and ocular dryness, which can be disabling; ocular signs including objective evidence for involvement; salivary gland involvement including abnormal appearance of salivary glands; and presence of antibodies to Ro and/or La. Patients may also experience severe, variable and unpredictable fatigue, which is similar in character and severity to that of patients with systemic lupus erythematosus (SLE). Similarly, fibromyalgia and widespread chronic pain are found in 5% of pSS patients, again, comparable to SLE. Extra-glandular manifestations occur in 20 to 40% of patients and include rashes, peripheral neuropathy, Hashimoto's thyroiditis, non-erosive arthritis, arthralgia, vasculitis, interstitial lung disease, B-cell lymphoma, pancreatitis, primary biliary cirrhosis, autoimmune hepatitis and renal disease.

BLyS (also known as BAFF) promotes B-cell maturation, proliferation and survival. Transgenic mice that over-express this cytokine develop features of SLE, and go on to develop clinical characteristics of primary Sjögren's syndrome [[Mackay, 1999](#)]. In recent years, several studies have focused on elucidating the role of BLyS in primary Sjögren's syndrome. Serum BLyS levels were demonstrated to be increased, and to correlate with, levels of anti-Ro/SS-A antibodies and rheumatoid factor (RF) in patients with primary Sjögren's syndrome [[Mariette, 2003](#)] and elevated levels of BLyS have been detected in saliva [[Daridon, 2007](#); [Lavie, 2008](#)].

Belimumab, an anti-BLyS therapy, has been studied in patients with Sjögren's syndrome. In the open label, Phase II BELISS trial of belimumab in patients (n = 30) with primary Sjögren's syndrome, 60% of subjects (18/30) met the primary endpoint - improvement in at least two of the following five parameters: dryness, fatigue, pain, systemic activity or B-cell biomarkers - measured at 28 weeks [Mariette, 2015]. This study will allow the opportunity to test the efficacy of belimumab in a placebo controlled, randomized trial and will extend the observations of the BELISS study in assessing the effects on disease activity in patients treated with belimumab for 12 months.

Rituximab, an anti-CD 20 therapy, has also been studied in patients with Sjögren's syndrome. In general, these studies - despite being heterogonous, especially with respect to the patient populations recruited - have shown evidence of temporary beneficial effects on symptoms of dryness and fatigue [Meijer, 2010; Devauchelle-Pensec, 2014; Dass, 2008]. Furthermore, additional studies have raised the possibility of rituximab positively impacting systemic disease, salivary histology and biomarkers such as beta2 microglobulin [Carubbi, 2014]. As a result, rituximab has been recommended as a potential treatment [Ramos-Casals, 2012] in subjects with systemic disease.

Administration of anti-CD20 therapy has been shown to result in an increase in serum BLyS [Cambridge, 2006; Lavie, 2007; Pers, 2007]. This increase is linked both to the disappearance of BLyS-binding B cells in peripheral blood, as well as to a true homeostatic feedback characterized by increased BLyS mRNA expression in monocytes after rituximab [Toubi, 2007; Lavie, 2007]. This increase in BLyS after rituximab could favor the stimulation of new autoimmune B cells and, possibly explains the waning clinical improvement over time seen in clinical studies of rituximab in patients with Sjögren's syndrome.

Anti-BLyS and anti-CD20 therapeutics operate through different but complementary mechanisms: anti-BLyS (e.g., belimumab) therapeutics rapidly increase peripheral memory B cells (possibly by mobilization/redistribution of tissue B cells), decrease naive, activated and plasma B cell subsets, and increase stringency on B cell selection during reconstitution; while anti-CD20 (e.g., rituximab) therapeutics eliminate peripheral B cells through complement dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Paired together, these two mechanisms may achieve synergistic effects through improved depletion of memory and germinal center tissue B cells and increased stringency during B cell reconstitution with additive effects through more efficient targeting of circulating plasma cells.

Pre-clinical evidence supporting the hypothesis that dual B-cell targeted immunotherapy maybe more efficacious than monotherapy, has been generated in a human-CD20 expressing mouse model. This model demonstrated limited tissue depletion with anti-CD20 antibody mono-therapy but increased efficacy of anti-CD20 therapy when B cells were mobilized into the peripheral blood through concomitant inhibition of adhesion [Gong, 2005]. The combined effect of administration of mouse BLyS receptor (BR3)-Fc and anti-hCD20 in this model leads to more effective tissue B cell depletion. Similar observations have been made in SLE models [Lin, 2015] where dual targeting resulted in greater efficacy with increased tissue B cell depletion, greater reduction in a range of auto-antibody levels and significant decreases in total IgG1, IgG2b, IgG3, IgM and IgA

when compared to BLyS inhibition and CD20 B-cell depletion alone. Total plasma cells in the long lived bone marrow niche, thought to be less sensitive to immunotherapy, were not affected relative to monotherapy with the exception of IgG1+ plasma cells.

Assessment of the translatability of the IgG reductions to humans are difficult to make due to species differences in B-cell biology and different treatments; however the mouse data raises the hypothetical risk that immunoglobulin levels may reduce more with combination treatment.

There also exists limited clinical evidence that dual B-cell targeted immunotherapy with both BLyS blockade and B cell depletion may be more efficacious than monotherapy. One subject in the BELISS trial [Mariette, 2015; De Vita, 2014] had severe refractory Sjögren's syndrome including parotid B-cell MALT lymphoma and cryoglobulinemic vasculitis. Previous treatment (prior to BELISS) with rituximab, steroids, cyclophosphamide, azathioprine, plasmapheresis, hyperbaric therapy and surgery had failed. Administration of belimumab to this patient in the BELISS study was also ineffective. However, 49 days after her last infusion with belimumab, the subject was again treated with rituximab. She experienced complete and sustained remission of her lymphoma, regression of her previously non-healing cutaneous ulcer and complete normalization of her serologic biomarkers. Although this is a limited, single-case study, it raises the possibility of profound effects achievable through concomitant exposure to anti-BLyS and anti-CD20 therapeutics.

### 3. OBJECTIVES AND ENDPOINTS

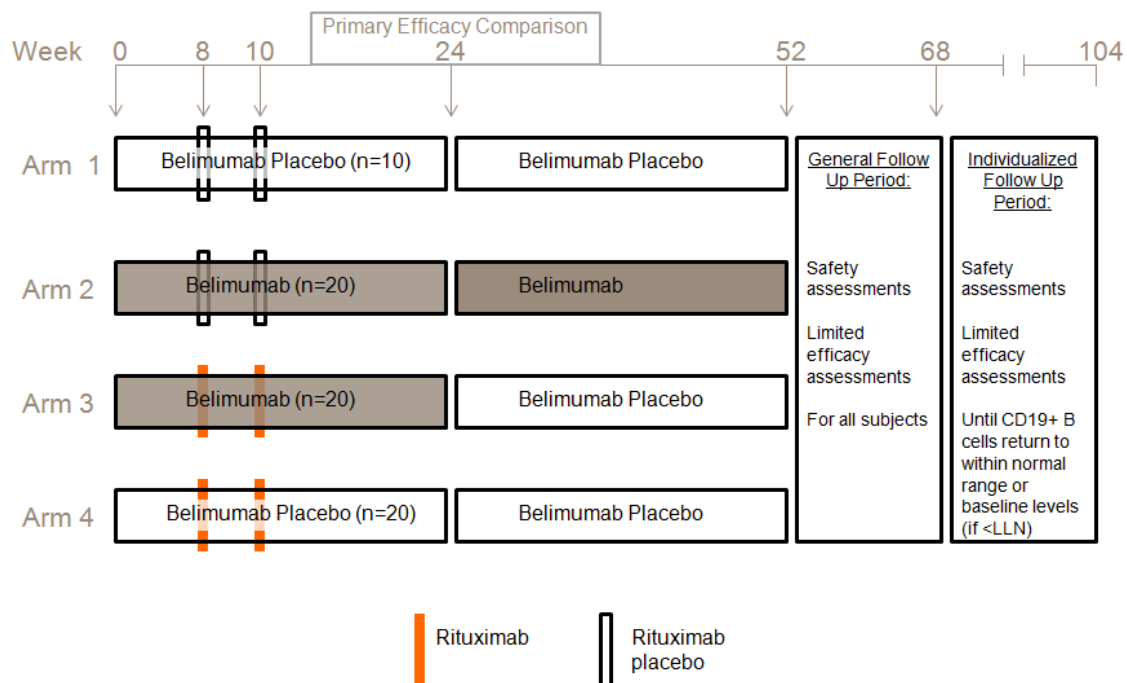
Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"> <li>Safety and tolerability of anti-BLyS / anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies</li> </ul>	<ul style="list-style-type: none"> <li>Safety and tolerability; including incidence of SAEs and AESIs.</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>Clinical efficacy of anti-BLyS / anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies</li> <li>Assessment of anti-BLyS / anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies on tissue B-cells.</li> </ul>	<ul style="list-style-type: none"> <li>ESSDAI score over time</li> <li>Stimulated salivary flow over time</li> <li>Oral dryness numeric response scale over time</li> <li>B cell quantification within salivary gland biopsy at Week 24</li> </ul>



Objectives	Endpoints
<b>Exploratory</b>	
<ul style="list-style-type: none"> <li>Assessment of mechanism and durability of effect of anti-BLyS/anti-CD 20 co-administration therapy and anti-BLyS and anti-CD20 monotherapies.</li> </ul>	<ul style="list-style-type: none"> <li>Ocular dryness numeric response scale over time</li> <li>Lacrimal gland function as measured by Schirmer's test.</li> <li>Physician's Global Assessment (PGA) of disease activity over time</li> <li>Serologic markers over time</li> <li>Change in peripheral blood leukocytes including B cell subsets over time</li> <li>BLyS levels in blood</li> <li>Immunogenicity of rituximab and belimumab</li> <li>Pharmacokinetics of rituximab and belimumab</li> <li>Change from baseline in the cellular composition of the salivary gland</li> <li>Sustained efficacy of anti-BLyS/anti-CD 20 co-administration at Week 52</li> <li>Additional exploratory biomarkers may be evaluated               <ul style="list-style-type: none"> <li>Transcriptomic analysis of blood and salivary gland</li> <li>B and T cell receptor clonal analysis in peripheral blood and salivary gland</li> <li>Proteomic assessment of the saliva</li> </ul> </li> </ul>
<b>Health Outcomes</b>	
<ul style="list-style-type: none"> <li>Gather preliminary information on patient reported outcomes of anti-BLyS/anti-CD 20 co-administration therapy and anti-BLyS and anti-CD 20 monotherapies</li> </ul>	<ul style="list-style-type: none"> <li>ESSPRI score (and individual scale sub-scores) over time</li> <li>Fatigue and Discomfort- SICCA Symptom Inventory (PROFAD SSI SF) over time</li> <li>Patient Global Assessment (PtGA) of disease activity over time</li> <li>Subject exit interviews</li> </ul>

## 4. STUDY DESIGN

### 4.1. Overall Design



This will be a multi-national, multi-center, double-blind (sponsor open) (see Section 6.3), randomized, placebo-controlled trial in subjects with active primary Sjögren's syndrome. The study design is shown in the schematic above.

This study is designed to understand the safety and tolerability profile of belimumab/rituximab co-administration and of belimumab monotherapy; and to evaluate whether either co-administration therapy or belimumab monotherapy has a substantive effect on disease activity. It is also designed to understand the underlying immunological mechanisms impacted by belimumab monotherapy compared to placebo or rituximab monotherapy and to determine if there is a mechanistic difference between monotherapy and co-administration therapy. Disease activity assessment at Week 52 will allow determination of whether any clinical effects of co-administration therapy achieved at Week 24 are sustained after discontinuation of therapy and/or whether chronic treatment with belimumab monotherapy is effective.

Study data will be reviewed in a confidential manner during the conduct of the trial. In line with routine pharmacovigilance, subjects' blinded safety data will be reviewed on an ongoing basis during the study conduct by an internal GSK Safety Review Team (SRT).

An internal GSK Safety Review Committee (iSRC), independent of the study team, will maintain governance of the study and will periodically review all available data in an un-blinded manner with a focus on key safety parameters. A Therapeutic Area (Immuno-Inflammation) Data Assessment Committee (TA DAC), independent of the study team, will periodically review un-blinded efficacy data and at the interim analysis will advise

the iSRC on adaptive design changes should such changes be required. An iSRC charter details the activities of these committees, including when and which data will be reviewed, how the integrity of the study will be maintained, and the membership of both committees. Once approximately half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy data will be evaluated. . Following the interim analysis, a number of actions could be mandated by the iSRC: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.

## **4.2. Treatment Arms and Duration**

Approximately 70 subjects will be recruited into the study initially. Withdrawals may be replaced. At Day 0, subjects will be randomized 1:2:2:2 to one of the four treatment arms below.

1. Placebo Arm: Approximately 10 subjects will receive belimumab placebo weekly subcutaneous injections to Week 52 and rituximab placebo infusions at Weeks 8 and 10.
2. Belimumab Monotherapy Arm: Approximately 20 subjects will receive 200 mg weekly subcutaneous injections of belimumab to Week 52 and placebo rituximab infusions at Weeks 8 and 10.
3. Co-administration Therapy Arm: Approximately 20 subjects will receive belimumab 200 mg SC weekly for 24 weeks followed by weekly placebo belimumab injections to Week 52 with rituximab 1,000 mg intravenously at Weeks 8 and 10.
4. Rituximab Monotherapy Arm: Approximately 20 subjects will receive 1,000 mg IV rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of placebo belimumab to Week 52.

The subjects will be stratified based on their baseline disease activity severity [ESSDAI 5-12 (moderate) vs. ESSDAI >12 (severe)] ensuring that within each disease severity there is an allocation across all treatment groups.

The total number of subjects recruited will be determined through an ongoing review of the data and sample size re-estimation. Following interim analysis, a number of actions could be taken: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 total subjects in the study where up to a maximum of 25, 45, 30 and 20 will be randomized to placebo, belimumab monotherapy, co-administration therapy and rituximab monotherapy respectively. The randomization ratio will vary dependent on the number of treatment arms continuing following the interim analysis.

### **4.3. Follow up Periods**

#### **4.3.1. General Follow up Period**

Subjects in all arms will receive investigational product (IP) until Week 52 (completion of the treatment phase). All subjects will enter a 16-week general follow-up period after the Week 52 visit or after discontinuation if a subject discontinues IP and withdraws from the treatment phase visits prior to Week 52. Assessments to be performed are included in the Time and Events Table, Section 7.1. During the general follow up period subjects will remain off of investigational product, endeavor not to change concomitant medication regimen, receive monthly safety follow up phone calls, and will return to the clinic for a site visit at the end of the general follow up period.

Monthly telephone calls for urine pregnancy test results, neurological questionnaire and to evaluate AEs, SAEs, and concomitant medications will be required during the 16-week general follow-up period.

#### **4.3.2. Individualized Follow up Period**

After completing the general follow-up period, subjects with CD 19+ B-cell levels below the lower limit of normal (or less than 90% of baseline, if baseline value was below LLN) will enter an individualized safety follow-up phase and return to the clinic for visits every 12 weeks with monthly calls between visits to evaluate subjects for any SAEs related to IP or study participation, fatal SAEs, and designated AESIs (i.e., infections, malignancies, or depression, suicide/self-injury), and to check concomitant medications. Each subject will be followed until either “normalization” of CD 19+ B cell count occurs or, at the investigator’s discretion the subject starts receiving disease modifying therapy that may affect B-cell numbers, or for up to a maximum of 2 years (i.e., up to Week 104) – whichever comes first. “Normalization” is defined as return of CD 19+ B cell count above LLN or within 10% of baseline (in cases where the baseline value itself was below LLN). When a decision is made for subjects to exit the individualized safety follow up phase, they will attend a final site visit within 28 days of that decision for final efficacy assessments to help explore the durability of any treatment response.

Subjects who prior to the Week 68 visit receive a disease modifying therapy that may affect B-cell numbers are not required to enter the IFU.

Finally, as this is an exploratory clinical trial and neither agent is licensed for Sjögren’s syndrome there are no plans to provide either agent following completion of the treatment phase of the study.

### **4.4. Type and Number of Subjects**

Adult subjects with symptomatic and systemically active disease as well as evidence of glandular reserve function will be recruited. A screen failure rate of 25% is anticipated. This implies 94 subjects must be screened in order to randomize approximately 70 subjects into the trial.

The total number of subjects randomized may increase following sample size re-estimation up to a maximum of 120 recruited into the study. The sample size re-estimation will be conducted at the interim analysis.

In addition, if subjects prematurely discontinue the study, additional subjects may be randomized and assigned to the next treatment in the randomization schedule at the discretion of the Sponsor.

#### **4.5. Design Justification**

This is a randomized, double-blind (sponsor open), placebo-controlled trial. Stable, low dose steroids ( $\leq 10$  mg prednisone or equivalent) and hydroxychloroquine will be permitted in all treatment arms. The use of pilocarpine and cevimeline (at stable doses) as well as symptomatic therapies (such as ophthalmic lubricants, chewing gum) may be used for symptom relief during the treatment and follow up phases but would be prohibited within a period of time prior to endpoint assessments (see Section 6.9.1 for details). Considering that there are no disease modifying treatments for Sjögren's syndrome and that approved therapies consist of symptomatic treatments, inclusion of a placebo-controlled arm is ethically justifiable – especially considering these subjects will be allowed to continue stable low doses of standard of care treatments (steroids, hydroxychloroquine and symptomatic topical therapies).

#### **4.6. Dose Justification**

##### Dose Selection:

The belimumab 200 mg SC weekly dose was selected because it delivers a substantial molar excess of belimumab above free BLyS levels in the blood, resulting in rapid suppression of BLyS levels and is understood to be equivalent (by area under the curve, AUC) to the belimumab 10 mg/kg IV dose which has been shown to be safe and effective in patients with active SLE. A Phase III study with 200 mg belimumab administered SC weekly in SLE patients is currently ongoing. The double blind phase of this study was recently completed; the belimumab 200 mg SC weekly dose plus standard of care significantly improved SLE Response Index (SRI) and decreased time to severe flare compared with placebo plus standard of care. Furthermore, safety findings with belimumab plus standard of care were similar to that of placebo plus standard of care [Stohl, 2017]. In addition, a completed belimumab trial in patients with Sjögren's syndrome [BELISS study; Mariette, 2015] used the 10 mg/kg IV dose without unexpected adverse events.

The rituximab 1,000 mg IV dose (x2, 2 weeks apart) was selected because it causes rapid depletion of peripheral B cells to below the lower limit of quantification. Also, this regimen is the approved treatment course for patients with rheumatoid arthritis (RA). In addition, published trials of rituximab in patients with Sjögren's syndrome have used this regimen.

### Dose Duration and Selection of Key Time Points:

In the co-administration therapy arm, rituximab treatment will commence at Week 8, two months after the start of belimumab. This will provide an opportunity to observe the anticipated increase in the memory B cell population in peripheral blood (mobilization endpoint) expected with belimumab and to determine whether greater increases in peripheral B cells correlate with greater efficacy for individual subjects in the co-administration therapy arm.

Following the last dose of rituximab therapy (which will be at Week 10 for the co-administration arm), B cell levels are predicted to remain suppressed below the level of quantification for at least 14 weeks [Emery, 2006; Meijer, 2010]. Therefore, Week 24 is a time point at which both anti-CD 20 and anti-BLyS pharmacodynamic effects are maximal, and was selected as the time point for primary efficacy comparison.

In the co-administration therapy arm, continuing belimumab treatment to Week 24 provides an opportunity to assess peripheral B cell reconstitution in the presence of prolonged BLyS suppression.

The Week 52 assessment provides an opportunity to determine whether treatment effects achieved at Week 24 in the co-administration therapy group can be maintained or improved after a drug-free follow up period (persistence of effect after treatment discontinuation) and to evaluate the effects of chronic (52 week) belimumab treatment on clinical, functional and mechanistic endpoints.

The primary efficacy comparison for this study at Week 24 will be between the co-administration therapy arm and the placebo arm.

## **4.7. Benefit:Risk Assessment**

Summaries of findings from both clinical and non-clinical studies conducted with GSK1550188 and rituximab can be found in the Investigator's Brochure and product label, respectively.

There is an unmet medical need in pSS for a disease modifying therapy that can prevent B-cell mediated autoimmune damage, alleviate glandular as well as constitutional symptoms, and ameliorate extra-glandular target organ manifestations. There are no disease-modifying treatments for this disease. Rituximab controlled trials have shown temporary but not sustained effects on glandular function and constitutional symptoms [Meijer, 2010; Devauchelle-Pensec, 2014]. In an open label belimumab study (BELISS, n=30) 60% of subjects met the primary endpoint defined as improvement in at least two of five parameters including dryness, fatigue, pain, measures of systemic disease activity and B cell biomarkers; however, the study did not demonstrate change in objective measures of glandular function [Mariette, 2015]. A single clinical case has been reported where sequential belimumab and rituximab appeared to yield dramatic results. The subject had severe refractory pSS including parotid B-cell MALT lymphoma and cryoglobulinemic vasculitis. While numerous previous treatments, including rituximab and belimumab monotherapy, had failed, the patient responded to therapy when

rituximab was administered 49 days following a treatment course of belimumab [De Vita, 2014].

The safety profile of belimumab in the open-label study described above appeared consistent with that in the SLE population. The safety profile of rituximab in pSS suggests an elevated incidence of serum sickness compared with RA, SLE or lymphoma [Meijer, 2010] and has ranged from 6-38% [Carubbi, 2014]. The increased risk could be related to the disease itself or less intensive background steroid/immunosuppressant regimens. Hypergammaglobulinemia, which is common in pSS, could also contribute.

Potential increased risks associated with the co-administration of belimumab and rituximab include more prolonged B-cell suppression and more profound hypogammaglobulinemia that could put subjects at increased risk for serious infections (including PML and Hepatitis B reactivation), malignancy, as well as greater interaction with immunizations.

There are no clinical trial data for the co-administration of belimumab with rituximab; however, the following data were reviewed and no new safety risks beyond what would be expected for either agent alone was suggested from the very limited data available from patients (n=39) who may have had overlapping exposures to belimumab and rituximab:

- The GSK Safety Database of adverse events from clinical trials and post-marketing experience
- An insurance claims database (SafetyWorks)
- In-stream, blinded data from an ongoing GSK study of belimumab in subjects with vasculitis who were induced with high dose corticosteroids and either rituximab or cyclophosphamide.

Given that the experience of co-administered anti-CD20 and anti-BLyS to date is very limited, coupled with the introduction of dual biologic therapy in this new indication of pSS, robust safety monitoring and stopping rules are being implemented to safeguard subject safety. The key risk assessment and mitigation strategy for this protocol is outlined in Section 4.7.1.

#### 4.7.1. Risk Assessment for Dual Biologics in pSS

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Investigational Product (IP) [belimumab (GSK1550188) &amp; rituximab]</b>		
<p><b>Infections:</b></p> <p>Prolonged B-cell suppression and more complete B-cell depletion expected; potential for more profound hypogammaglobulinemia with increased risk for serious infections including opportunistic infections (OIs), PML, and HBV re-activation.</p>	<p><i>Rituximab:</i> The rate of serious infections with rituximab in the RA population is 4/100 per year.</p> <p>Reactivation of hepatitis B has also been very rarely reported in RA patients receiving rituximab.</p> <p>Late onset neutropenia occurs rarely in patients treated with rituximab.</p> <p><i>Belimumab:</i> The rate for belimumab in SLE is 5% of subjects receiving either belimumab or placebo.</p> <p><i>Belimumab and Rituximab:</i> Infections are expected events for both belimumab and rituximab.</p> <p>Cases of PML have been very rarely reported, including fatal events, for both rituximab and belimumab in autoimmune diseases.</p> <p><i>Dual Belimumab and Rituximab:</i> There is pre-clinical evidence for prolonged B-cell suppression and more complete B-cell depletion as well as effect on IgG1+ plasma cells in the long-lived bone marrow niche thought to be less sensitive</p>	<p>Exclusions based on significant infection history, serologic evidence of past or present HBV or HCV infection; IgG &lt; 550 mg / dL, IgA deficiency, neutrophils &lt;1.5X10<sup>9</sup>/L.</p> <p>A PML management plan including neurologic questionnaire and patient alert card.</p> <p>Individual subject's treatment will be discontinued for (a) life-threatening infection; (b) IgG &lt;400mg/dL (or &lt;550mg/dL if associated with a serious infection); (c) neutrophils &lt; 1X10<sup>9</sup>/L</p> <p>Subjects will be monitored for up to 2 years or until B-cells return to LLN and monitored for late onset neutropenia at 6 months post-rituximab.</p>



Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>to immunotherapy [Lin, 2015] with dual B-cell immunotherapy.</p> <p>Assessment of the translatability of the IgG reductions to humans is difficult to make due to species differences in B-cell biology and different treatments; however, the mouse data raises the hypothetical risk that immunoglobulin levels may reduce more with co-administration treatment.</p>	
<p><b><u>Systemic Infusion / Injection Reactions, Hypersensitivity Reactions and Immunogenicity</u></b></p> <p>There is a potential risk for increased ADA due to cross reactivity which could lead to increased frequency of hypersensitivity reactions, particularly of the delayed type.</p> <p><u>Serum Sickness:</u> The incidence of serum sickness associated with rituximab is higher in autoimmune indications and likely greater in Sjögren's Syndrome vs. RA [Meijer, 2010].</p>	<p><i>Rituximab:</i> The incidence of serum sickness associated with rituximab in pSS studies has ranged from 6-38% [Carubbi, 2014].</p> <p><i>Belimumab and Rituximab:</i> Administration of belimumab and rituximab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Delay in the onset of serious hypersensitivity reactions can occur. Both rituximab and belimumab have been associated with delayed type non-acute HSR/serum sickness, although no relationship to ADA has been established.</p> <p><i>Dual Belimumab and Rituximab:</i> Incidences of hypersensitivity and infusion reactions have been noted to be higher with co-administration vs.</p>	<p>ADA will be monitored with collection at baseline, Weeks 8, 24, and 52</p> <p>A pre-medication regimen will be given before each rituximab/rituximab placebo infusion: methylprednisolone 100 mg IV, an oral antihistamine and analgesic.</p> <p>Patients will be given an alert card for HSR and delayed HSR/serum sickness.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	mono-biologic therapy but no association with ADA has been established [ <a href="#">Weinblatt, 2006</a> ].	
<p><b><u>Malignancy</u></b></p> <p>There is an increased risk of B-cell lymphoma in pSS. There is a theoretical increased risk of malignancy with combination immunosuppressive mechanisms; however, the potential synergistic effect of rituximab/belimumab would be assumed to result in a prolonged b-cell depletion that would not be dissimilar to repeat doses of rituximab.</p>	<p><i>Belimumab and Rituximab:</i> Immunomodulatory drugs like rituximab and belimumab may increase the risk of malignancy. To date, no causal relationship to belimumab or rituximab to malignancy, including B-cell lymphoma, has been detected with either agent, both of which have been administered long term and in combination with other immunosuppressants of various mechanisms.</p>	<p>Subjects with a history of malignancy in the 5 yrs prior to randomization will be excluded (see Section <a href="#">5.2</a>, criterion #4).</p>
<p><b><u>Interaction with Vaccinations</u></b></p> <p>There is a risk of reduced antibody titers with mono and dual B cell immunotherapy. The potential synergistic effect of rituximab and belimumab may result in a prolonged B-cell depletion that should have a similar impact on vaccine response as administering repeated doses of rituximab.</p>	<p><i>Rituximab:</i> Median antibody titers (tetanus, diphtheria, pneumococcus) at Week 32 were reduced from baseline in atacicept but not placebo-treated patients who had been previously treated with rituximab. However, these values recovered close to baseline by Week 16 of the follow-up, there were few shifts to below protective titres, and no between-group differences with respect to the frequency of shifts.</p> <p><i>Belimumab:</i> the efficacy of concurrent vaccination in patients receiving belimumab is not known;</p>	<p>Live vaccination is prohibited from 30 days prior to Day 0 until the end of the general follow up period or IFU, if appropriate.</p> <p>Subjects' vaccination status should be assessed and current immunization guidelines followed; all necessary vaccinations should be administered if possible no later than 30 days prior to Day 0.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>however, in the belimumab vaccination trial (study 115470, see GSK Clinical Study Register at <a href="http://www.gsk-clinicalstudyregister.com">www.gsk-clinicalstudyregister.com</a>), evaluation of the impact of belimumab treatment on response to on-treatment vaccination with 23-valent pneumococcal vaccine revealed that immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.</p>	
<p><b><u>Psychiatric Events</u></b></p> <p>There is a potential risk of psychiatric events with belimumab and rituximab.</p>	<p><i>Rituximab:</i> Depression and anxiety were common adverse events in rituximab RA trials.</p> <p><i>Belimumab:</i> There have been reports of depression and suicidality in patients receiving belimumab. A causal relationship to belimumab has not been established.</p>	<p>Subjects who, in the investigator's opinion, pose a significant suicide risk will be excluded.</p> <p>The C-SSRS will be completed at each visit during which the subject may potentially be exposed to belimumab.</p> <p>Subjects will be monitored closely for signs and symptoms of psychiatric illness including depression and suicidal ideation. Subjects displaying such signs and symptoms will be treated appropriately and referred as necessary to specialty psychiatric care.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b><u>Cardiac disorders</u></b>	<p><i>Rituximab:</i> Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. There is no data on the safety of rituximab in patients with moderate to severe heart failure or severe, uncontrolled CV disease.</p> <p><i>Belimumab and Rituximab:</i> Hypotension may accompany infusion/post-injection systemic reactions with both rituximab and belimumab.</p>	<p>Exclude subjects with severe heart failure (New York Heart Association, Class IV) or other severe, uncontrolled cardiac disease.</p> <p>Closely monitor any patients with cardiac history or those who have experienced prior cardiopulmonary adverse reactions during administration of rituximab/rituximab placebo. Consider withholding anti-hypertensive medications 12 hours prior to rituximab/rituximab placebo infusion.</p>
<b><u>Skin reactions</u></b>	<p><i>Rituximab:</i> Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome; some with fatal outcome, have been reported with rituximab.</p>	<p>Permanently discontinue treatment in the case of such an event with suspected relationship to treatment.</p>
<b><u>Posterior Reversible Encephalopathy Syndrome (PRES)</u></b>	<p><i>Rituximab:</i> Cases of PRES / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS</p>	<p>Medical monitor will be notified of any new neurologic symptoms (see Section 5.4.3). Medical monitor and investigator will consider the possibility of PRES in differential diagnosis.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.	
<b>Study Procedures</b>		
<b><u>Salivary gland Biopsy</u></b> This procedure is associated with (a low) incidence of complications including bleeding and hematoma formation.	The reported incidence of bleeding and hematoma were 7.5% and 2.7%, respectively in a large case series [ <a href="#">Santiago</a> , 2012].	Subjects will be instructed to stop anticoagulant therapy (i.e., aspirin, NSAIDs, warfarin) prior to the procedure. Also, the biopsy will be performed by qualified physicians, surgeons or dentists and the personnel performing the biopsy will be required to undergo study-specific training in the performance of this procedure.

#### 4.7.2. Vaccinations

The vaccination risk mitigation strategy detailed in the table above recommends that all necessary vaccinations should be administered if possible no later than 30 days prior to day 0 and requires that no live vaccine be given from 30 days prior to day 0 until the end of the general follow up period or IFU, if appropriate. In determining which vaccinations are necessary, investigators should follow guidelines such as the EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases ([van Assen](#), 2011). If indicated for standard of care, non live vaccines (e.g., inactivated influenza vaccines) may be administered while on study based on an assessment of the benefit:risk (e.g.: theoretical risk of decreased responsiveness).

#### 4.7.3. Benefit Assessment

This study provides an opportunity for subjects with moderate to severely active Sjögren's syndrome to benefit from a potentially disease modifying regimen that may stop B-cell mediated autoimmune damage, alleviate glandular as well as constitutional symptoms, and ameliorate extra-glandular target organ manifestations. Additionally this

study is designed for active Sjögren's syndrome patients who are not experiencing relief despite their current medications, including topical symptomatic medications, oral muscarinic agonists, steroids and hydroxychloroquine (which are permitted in all arms) to benefit from the addition of potentially beneficial biological therapy.

#### **4.7.4. Overall Benefit:Risk Conclusion**

Taking into account the measures that will be implemented to minimize risk to subjects participating in this study, the potential risks associated with belimumab and rituximab are justified by the anticipated benefits that may be afforded to patients with Sjögren's syndrome who choose to participate in this trial.

## **5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA**

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement and product label.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

### **5.1. Inclusion Criteria**

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Age $\geq 18$ years, at the time of signing the informed consent.
TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Documented Primary Sjögren's Syndrome by American European Consensus Group criteria including: - either SS-A or SS-B positive.
3. Baseline unstimulated salivary flow $>0.0$ mL/min or evidence of glandular reserve function (stimulated baseline salivary flow $>0.05$ mL/min).
4. Symptomatic oral dryness ( $\geq 5/10$ on subject completed Numeric Response Scale)
5. Systemically active disease, ESSDAI $\geq 5$ points.
OR (for sites in ITALY ONLY) Systemically active disease, ESSDAI $\geq 5$ points and with at least: a) 1 extraglandular domain moderate,

OR

b) 2 extraglandular domains low.

## SEX

6. Male and female subjects; females of child bearing potential are eligible if using effective contraception:

Female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotropin (hCG) test), not lactating, and at least one of the following conditions applies:

- a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
    - Documented tubal ligation
    - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
    - Hysterectomy
    - Documented Bilateral Oophorectomy
  - Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study; otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
- b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication up to Week 68 after Day 0.

**GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)**

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Combined estrogen and progestogen oral contraceptive

- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

#### INFORMED CONSENT

7. Ability to understand and comply with the protocol-required procedures and provision of informed consent.

#### OTHER CRITERIA

8. For **FRANCE ONLY**, a subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category. It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

## 5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

#### CONCURRENT CONDITIONS/MEDICAL HISTORY

1. Diagnosis of secondary Sjögren's syndrome.
2. Active life-threatening or organ-threatening complications of SS disease at the time of screening based on treating physician evaluation including but not restricted to (a) vasculitis with renal, digestive, cardiac, pulmonary or CNS involvement characterized as severe, (b) active CNS or PNS involvement requiring high dose steroids, (c) severe renal involvement defined by objective measures, (d) lymphoma.
3. History of major organ transplant (including hematopoietic stem cell transplant).
4. History of malignancy within past 5 years [with the exception of adequately treated: (a) cervical carcinoma Stage 1B or less, (b) non-invasive basal cell and squamous cell skin carcinoma].
5. History of infection requiring long term systemic therapy including: (a) history of positive HIV serology, (b) positive serology for Hepatitis C (HCV), (c) positive serology for Hepatitis B (HB), defined as: (i) HB surface antigen positive (HBsAg+)



OR (ii) HB core antibody positive (HBcAb+).

6. Previous serious opportunistic or atypical infections or hospitalization for treatment of infection within 364 days of Day 0 or use of parenteral (IV or IM) antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 364 days of prior to Day 0.
7. Patients in a severely immunocompromised state.
8. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
9. History of significant medical illness (or planned surgical procedure) which in the opinion of the investigator would interfere with the study procedures and / or assessments - including but not limited to IgG4 disease or prior head or neck irradiation.
10. Severe heart failure (New York Heart Association, Class IV) or other severe, uncontrolled cardiac disease.
11. Tuberculosis (TB), defined as: (a) prior history of TB infection, (b) suspicion of TB infection or (c) current TB infection.
12. At risk of suicide, as indicated by a lifetime history of attempted suicide or significant suicidal ideation over the 6 months prior to the screening visit; or, if in the Investigator's judgment, the subject is at risk for a suicide attempt.
13. Neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML) - not otherwise explained - or confirmed PML.
14. Electrocardiogram (ECG) showing a clinically significant abnormality at Screening or showing an average QTcB or QTcF interval  $\geq 450$  msec ( $\geq 480$  msec for subjects with a Bundle Branch Block) over 3 consecutive ECGs (refer to Section 7.4.5)
15. ALT  $> 2 \times \text{ULN}$  and bilirubin  $> 1.5 \times \text{ULN}$  (isolated bilirubin  $> 1.5 \times \text{ULN}$  is acceptable if bilirubin is fractionated and direct bilirubin  $< 35\%$ ).
16. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

#### CONCOMITANT MEDICATIONS

17. Use of systemic immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), mizoribine, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, 6-mercaptopurine, or thalidomide) within 60 days prior to Day 0.
18. Have received cyclophosphamide within 180 days prior to Day 0.
19. Have received anti-BLyS, anti-CD 20, anti-CD22 or anti-CD52 or any other B-cell depleting agent within 364 days prior to Day 0.
20. Have received abatacept or any biologic agent within 180 day prior to Day 0
21. Have received IVIG or plasmapheresis within 90 days prior to Day 0.
22. Have received oral steroid  $> 10$  mg prednisone equivalent/day within 30 days prior to

Day 0 or oral steroid >20 mg prednisone equivalent / day for a minimum of two consecutive weeks within 60 days prior to Day 0. Have received parenteral steroid within 60 days prior to Day 0.

23. Have received a live vaccine within 30 days of Day 0.
24. Current participation in any other interventional trial.
25. Planned blood donation during the treatment and follow up periods of the study.

#### RELEVANT HABITS

26. Subjects who are unable or unwilling to administer, or to have a caregiver administer subcutaneous injections.
27. Drug or alcohol abuse or dependence.

#### CONTRAINDICATIONS

28. History of hypersensitivity to belimumab and/or rituximab or known to have titers of human anti-mouse antibody or human anti-chimeric antibody or history of hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

#### DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

29. Have an IgA deficiency (IgA level <10 mg/dL).
30. Any of the following screening laboratory values:
  - White blood cells (WBC) <2 x 10<sup>9</sup>/L
  - Neutrophils <1.5 x 10<sup>9</sup>/L
  - Circulating IgG < 550 mg / dL
  - Aspartate aminotransferase (AST) >2.0 times the upper limit of normal
  - Alkaline phosphatase (ALP) >1.5 times the upper limit of normal
  - Bilirubin >1.5 times the upper limit of normal (unless direct bilirubin fraction is < 35%)
  - CD 19+ B-lymphocyte counts <0.1 x 10<sup>9</sup>/L (<100 per CMM) (applies only to subjects previously exposed to B cell depleting therapies)
31. For **FRANCE ONLY**, subjects with legal or administrative guardianship (“tutelle” or “curatelle”), or subjects deprived of liberty, or subjects receiving psychiatric care, or subjects hospitalized in an Health and Social Establishment for purposes other than participation in this study.

### 5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failures meet the Consolidated Standards of Reporting Trials publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

**Rescreening:** Subjects who fail screening may be rescreened once at the discretion of the investigator.

**Repeat assessments during the 35 day screening period:** assessments (see Section 7.1), including laboratory assessments, may be repeated if determined necessary by the investigator, for example: (a) in cases of technical malfunction (e.g., loss of laboratory specimen), (b) in the event of a value close enough to the exclusionary threshold that it may reasonably lie within the degree of variability of the assay; (c) if there is reason to believe the result may be false (i.e.: contradicts recent result for the same parameter). These are repeat assessments and not rescreening events. If the original result was exclusionary and is confirmed by repeat testing, the subject will be excluded.

In the specific case of an indeterminate result from autoantibody (SS-A, SS-B) assessment during the 35 day screening period, this assessment may be repeated once. If the result from the repeat assessment is either indeterminate or negative, the subject will be excluded.

### 5.4. Withdrawal/Stopping Criteria

#### 5.4.1. General Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or

administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

If a subject experiences a clinically significant AE that the investigator believes may be definitely, possibly or probably related to study agent and could potentially be exacerbated by the next dose, the investigator may delay IP dosing by up to one week or withhold one dose (or single dose co-administration). If a similar concern is present at the time of the next scheduled dose, the investigator should contact the Medical Monitor to determine whether treatment with belimumab or rituximab should be discontinued.

Subjects who discontinue IP (i.e., during the treatment phase prior to Week 52) should be encouraged to continue to participate in study visits in accordance with the Time and Events schedule, especially all remaining safety evaluations. All subjects, including those who decline to complete the treatment phase visits through Week 52, are required to participate in the general follow up phase (and the individualized follow up phase, if applicable).

In addition, for a subset of subjects who receive rituximab/placebo at the Week 8 visit, or at both the Weeks 8 and 10 visits, but who discontinue treatment prior to Week 46, maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until approximately 52 weeks after the last dose of rituximab/pbo was administered.

Week 46 is an important threshold for withdrawal as it is only beyond week 46 that continued exposure to belimumab/placebo dictates a longer follow up for pregnancy evaluation (Section [7.4.2](#)).

Subject discontinues treatment before the Week 8 Visit	Subject discontinues treatment after the Week 8 Visit and before Week 46	Subject discontinues treatment at or after Week 46
<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until approximately 52 weeks after the last dose of rituximab/pbo was administered.</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>

Please refer to Section 5.4.4 of the study reference manual for further consideration of scenarios which may be encountered in terms of the timing and circumstances of subject withdrawal and the steps which need to be followed.

#### 5.4.2. Early Withdrawal Visit

Subjects that withdraw consent prior to the week 68 visit should, if possible, complete an early withdrawal visit. The early withdrawal visit is identical to the week 68 visit (see Section 7.1) but also includes the exit interview (Section 7.3.1).

#### 5.4.3. Detailed Adverse Event Criteria

All subjects should be monitored closely for infection. Patients who develop IgG <400 mg/dL confirmed by repeat test 1 week (>2 days) after the initial result, will be withdrawn from study treatment. In addition, increased vigilance for infection is recommended in subjects who develop IgG <550 mg/dL. Those with a decrease in IgG below 550 mg/dL that is associated with a serious infection (i.e., an infection reported as

an SAE) will be withdrawn from study treatment. In addition, any subject who develops a life-threatening infection, regardless of IgG status, will be promptly withdrawn from IP. Finally, subjects will be withdrawn from study treatment for the following lab abnormality: neutrophils  $<1 \times 10^9/L$  (confirmed by repeat test 1 week [ $>2$  days] after the initial result).

A questionnaire-based neurological examination to detect any signs or symptoms consistent with the diagnosis of PML will be conducted at each visit (see [Appendix 5](#)). If any question is answered 'yes' and the reason for the symptom is unknown (i.e., is not definitely explained by other known cause), the subject will be referred to a neurologist for evaluation. An MRI with gadolinium enhancement (pending renal function evaluation) and/or cerebrospinal fluid (CSF) JCV PCR are recommended to be performed to confirm the diagnosis. In addition, the investigator should contact the Medical Monitor within 2 business days if any question is answered 'yes,' regardless of suspected cause, to discuss appropriate management of the patient. If PML is confirmed, investigational product will be discontinued.

Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported with the use of rituximab. In case of such an event with a suspected relationship to IP, treatment should be permanently discontinued.

A subject will be withdrawn from study treatment if he or she meets liver stopping criteria (defined below), presents with suicidal ideation of type 4 or 5 on the C-SSRS or, if in the investigator's judgment, the subject is at risk for a suicide attempt. Female subjects who become pregnant will be withdrawn from IP but may continue in the trial for safety reporting and outcomes assessments, including infant status.

Lymphoma discovered on evaluation of baseline biopsy post randomization is a finding to be reviewed by the GSK medical monitor and investigator but does not necessarily mandate subject withdrawal.

#### **5.4.4. Study Stopping Criteria**

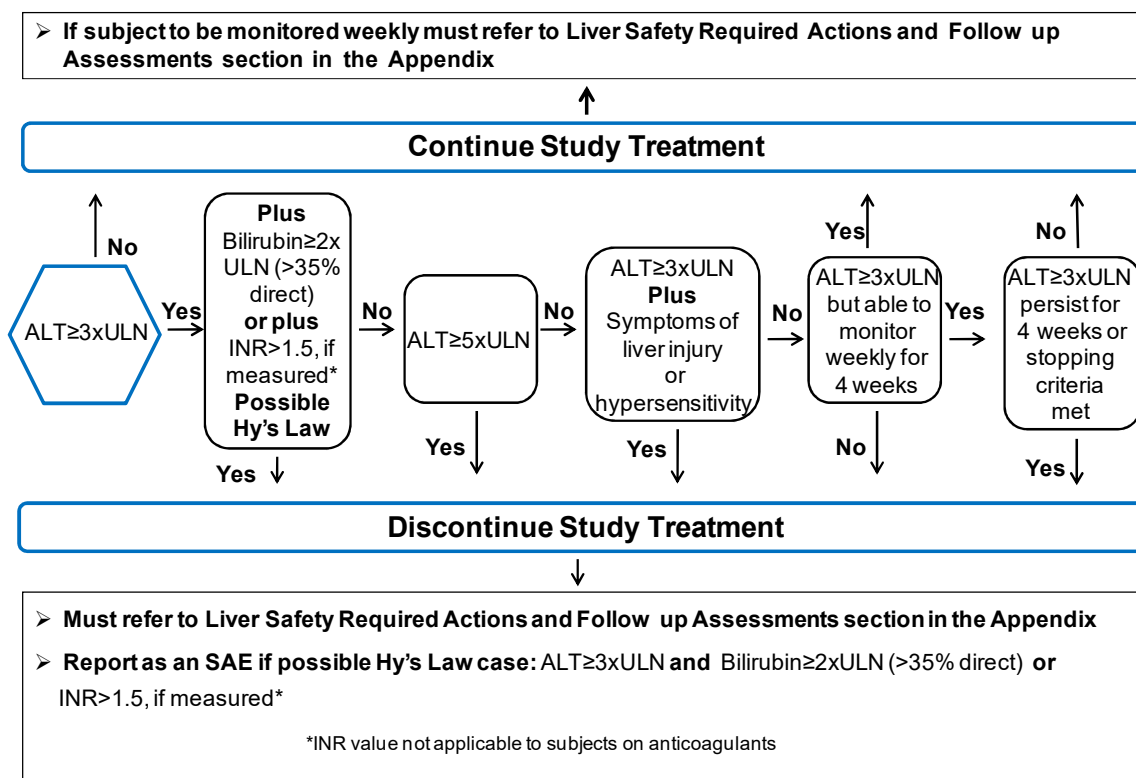
The un-blinded iSRC will review the safety data on a regular basis. The study would be stopped if 2 of the first 5 co-administration therapy (belimumab + rituximab) subjects to complete Week 10 have IgG  $<400$  mg/dL (confirmed by repeat test 1 week ( $>2$  days) after the initial result) that is associated with a serious infection or if there are 2 fatal infections. After this point, the un-blinded iSRC will stop the study if the rate of IgG  $<400$  mg/dL associated with serious infection or fatal infection rate exceeds 20% in the co-administration therapy arm.

#### **5.4.5. 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).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

## Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



The Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 2](#).

### 5.4.5.1. Study Treatment Restart

If a subject meets liver chemistry stopping criteria, do not restart subject with study treatment unless:

- GSK Medical Governance approval is **granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

Refer to [Appendix 3](#) for full guidance.

## 5.5. Subject and Study Completion

A completed subject is one who has completed the treatment and general follow up phase of the study including the final visit at Week 68 as defined in the Time and Events Table.

The end of the study is defined as the last subject's last visit.

## **6. STUDY TREATMENT**

### **6.1. Investigational Product and Other Study Treatment**

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the co-administration of those study treatments. Two investigational products, belimumab and rituximab, will be utilized in this study.

#### **6.1.1. Belimumab**

The trade name is Benlysta. The generic (USAN/INN) name is belimumab; the GSK code for the drug is GSK1550188. Belimumab is a recombinant, fully human, IgG1 $\lambda$  monoclonal antibody which is specific for soluble human B lymphocyte stimulator (BLyS, also referred to as BAFF and TNFSF13B). Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Belimumab drug product is provided as a 200 mg sterile, liquid product in a prefilled syringe containing a safety shield. Each syringe contains 1.0 mL (deliverable) of 200 mg/mL belimumab in 0.65 mg/mL L-histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 0.1 mg/mL polysorbate 80, with pH 6.0. Each syringe is single use.

The placebo control is provided as a sterile liquid product in a prefilled syringe containing a safety shield. Each syringe contains 1.0 mL (deliverable) of 0.65 mg/mL L-histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 0.1 mg/mL polysorbate 80, with pH 6.0. Each syringe is single use.

Belimumab should be stored in a refrigerator at 2-8°C with protection from light. Placebo should be stored in a refrigerator at 2-8°C with protection from light.

The first two doses of belimumab/placebo will be administered under supervision in the clinic with monitoring of subjects in clinic for 3 hours following the first and second dose. A patient alert card should be sent home with the subject each time belimumab/placebo is dispensed for home administration.

Detailed instructions on the storage and administration of study agent will be provided to the study site in the Pharmacy Manual and to subjects in a patient-friendly format.

#### **6.1.1.1. Self Administered Subcutaneous Injections and Log Book**

On Day 0, the subject will be randomized. Qualified study site personnel must review study agent handling and administration techniques with the subject prior to the first self-injection of the study agent. Subject will self-administer the study agent by SC injection, under supervision at the study site for the first administration on Day 0 and the second administration at Day 7 ( $\pm 1$  day). In the post-marketing setting with IV belimumab, delayed onset of symptoms of acute hypersensitivity reactions has been observed.



Subjects will remain at the clinic for 3 hours following the first and the second dose of belimumab/placebo for observation. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. At the discretion of the investigator, subjects who are adequately trained will self-administer all subsequent doses at home following the instructions provided on the dosing cards. After the first and the second 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 should not administer the study agent until they receive proper training in subcutaneous injection technique.

Subjects will be provided with a self-injection log book (refer to Appendices of Study Reference Manual). Subjects will fill out the injection log immediately after administering the injection, recording the date of injection, the injection site and whether or not the entire dose was administered. If the entire dose was not administered, an explanation should be provided, and the estimated amount injected should be recorded. The injection site should be rotated between the left or the right thigh and the abdomen. Dosing compliance should be reviewed with the subject monthly at the site study visit and self-injection log books reviewed by study site staff. Subjects are also required to return all unused syringes at each study visit. Used syringes should be placed in a sharps container and returned to the site as described in Section 2 of the Study Reference Manual.

#### **6.1.1.2. Missed Doses**

Study agent should be administered weekly. If the subject misses 3 or more consecutive doses the missed doses must be documented as a protocol deviation, the next dose should be administered at the study site and the subject should remain at the clinic for 3 hours following the injection for observation.

#### **6.1.2. Rituximab**

The trade name is MabThera or Rituxan. The generic (USAN/INN) name is rituximab. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange.

Rituximab is a 500 mg concentrated solution which requires dilution prior to infusion. It is a clear, colorless liquid. Rituximab and placebo (0.9% NaCl, sterile, pyrogen free) will be prepared at the study site by an unblinded pharmacist according to the procedure defined in the Pharmacy Manual. Rituximab treatment will consist of two 1000 mg intravenous infusions, a first 1000 mg intravenous infusion followed by a second 1000

mg intravenous infusion 2 weeks later. Please refer to the study reference manual for guidance regarding missed doses of rituximab.

Rituximab/placebo will be administered intravenously by an experienced healthcare professional under physician supervision, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an oral anti-pyretic and an oral antihistamine, e.g., paracetamol and diphenhydramine (approximately 60 minutes prior to rituximab) and intravenous methylprednisolone (100 mg) (at least 30 minutes prior to rituximab), will be given before each administration of rituximab/placebo.

The rituximab/placebo solution prepared by the unblinded pharmacist should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. As detailed in the rituximab summary of product characteristics, patients should be closely monitored for the onset of infusion reactions during the rituximab/placebo infusion. Vital signs (heart rate, blood pressure, temperature and respiratory rate) should be regularly measured and subjects should be observed closely for any signs that might be consistent with a hypersensitivity reaction (e.g. development of skin rash, fever). Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion interrupted immediately. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of clinical investigations including laboratory values. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

First infusion (Week 8):

The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Second infusion (Week 10):

Rituximab can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

Subjects will remain at the clinic for 1 hour following the first and the second dose of the rituximab for observation. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate based on clinical judgement. Subjects should be made aware of the potential risks, the signs and symptoms of a reaction, and the importance of immediately seeking medical attention. Patients treated must be given the patient alert card after each infusion of rituximab or rituximab placebo.

Refer to the Pharmacy Manual for detailed instructions on the administration and storage of rituximab.

## 6.2. Treatment Assignment

Subjects will be assigned to the relevant treatment, as outlined below, in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using the validated internal software RandAll NG. The randomization will be centrally controlled.

Subjects will be assigned to either the co-administration arm (A), belimumab arm (B), rituximab arm (C), or placebo arm (P) initially in a 2:2:2:1 ratio. A description of each regimen is provided in the table below:

Treatment Code	Treatment Description
A	Co-administration therapy
B	Belimumab 200 mg SC injection
C	Rituximab 1,000 mg IV infusion
P	Placebo

The subjects will be stratified based on his/her baseline disease activity severity [ESSDAI 5-12 (moderate) vs. ESSDAI >12 (severe)] ensuring that within each disease severity there is an allocation to each treatment group.

Note that the randomization allocation ratio may change following the interim analysis if it is decided that one or more treatment arms are dropped or the sample size within a treatment arm is increased.

## 6.3. Blinding

This will be a double blind (sponsor open) study and the following will apply:

- All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the subject will be blinded to the treatment allocated to individual subjects until the primary and follow up analyses have been completed (see Section 9.4.1).
- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.

- The date and reason for the unblinding must be fully documented in the eCRF.
- An unblinded pharmacist will be used at each study site to prepare rituximab and its placebo for intravenous administration. Unblinded monitors will be assigned to review all pharmacy records, storage and procedures.
- An unblinded member of staff at each site will be assigned to use the randomization software (RAMOS NG) and to receive all drug shipments and notifications.
- Following discussion with GSK medical monitor, a subject may continue in the study if that subject's treatment assignment is unblinded. The primary reason for unblinding (the event or condition which led to the unblinding) will be recorded in the eCRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- During the treatment and follow up phases (see Section 4.3.1 and Section 4.3.2), all study staff (which includes the investigator, sub-investigators, other site trial staff, and the subject) will remain blinded to central laboratory data that have the potential to unblind a subject's treatment assignment. Such data may include but is not necessarily limited to:
  - B-cell lymphocyte counts including results from flow cytometry
  - IgM and IgA levels

Refer to the central laboratory manual for additional information.

- The iSRC will perform safety reviews of laboratory data during the conduct of the study, as outlined within the iSRC charter.
- Sponsor open refers to those members of the iSRC and the TA DAC who are unblinded, as outlined in the iSRC charter. The GSK study team will remain blinded until the primary analysis (see Section 9.4.1) except for those in unblinded roles e.g., unblinded monitor for monitoring the pharmacy etc, as well as a restricted number of team members required for interpretation of data at the interim analysis (Section 9.3.2), as specified in the iSRC Charter.

#### **6.4. Packaging and Labeling**

The contents of the label will be in accordance with all applicable regulatory requirements.

#### **6.5. Preparation/Handling/Storage/Accountability**

A description of the methods and materials required for preparation of and reconstitution of rituximab and its placebo will be detailed in a Study Specific Technical Agreement/Memo or Pharmacy Manual which will be accompanied by a Quality Agreement.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure, notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## **6.6. Compliance with Study Treatment Administration**

When subjects are dosed at the investigative site with belimumab or matching placebo subcutaneously, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When subjects self-administer study treatment(s) at home, compliance with belimumab or matching placebo treatment will be assessed through review of the self-injection log book with the subject during site visits and documented in the source documents and eCRF. A record of the number of belimumab syringes dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

Rituximab will be intravenously administered to subjects at the site. Administration will be documented in the source documents and reported in the eCRF.

## **6.7. Treatment of Study Treatment Overdose**

For this study, any dose of subcutaneous belimumab in excess of 200 mg per week ( $7 \pm 2$  days) will be considered an overdose. GSK does not recommend specific treatment for an overdose.

For this study, any dose of rituximab in excess of 1,000 mg IV within a 24 hour period will be considered an overdose. Please refer to the rituximab approved product label for advice on the management of overdose.

In the event of an overdose, the investigator or treating physician should:

1. contact the Medical Monitor immediately
2. monitor the subject closely for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities.
3. obtain a sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis)
4. document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor and based on the clinical evaluation of the subject.

## **6.8. Treatment after the End of the Study**

Subjects will not receive any additional treatment from GSK after completion of the study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

## **6.9. Concomitant Medications and Non-Drug Therapies**

### **6.9.1. Permitted Medications and Non-Drug Therapies**

- Oral steroids (provided subject is on a stable regimen for at least 30 days at a dose no greater than 10 mg prednisone equivalent daily prior to Day 0 and continues this dose for the duration of the study).
- Hydroxychloroquine (provided subject is on a stable regimen no greater than 400 mg po qd (ie daily) for 30 days prior to Day 0 and continues this dose for the duration of the study).
- Topical symptomatic therapies are detailed below:
  - Ophthalmic lubricants [(e.g. glucane or saline eye drops); subjects will be required to withhold dosing 4hrs prior to efficacy assessments].
  - Ophthalmic lubricating ointments [(e.g. Dry Eyes, LacriLube); subjects will be required to withhold dosing 24hrs prior to efficacy assessments].
  - Hydroxyl cellulose ophthalmic insert [(e.g. Lacrisert); subjects will be required to withhold dosing 24hrs prior to efficacy assessments].

- Non-pharmacologic saliva stimulants [(e.g. gums, drinks, teeth washing); subjects will be required to withhold dosing 90 minutes prior to efficacy assessments].
- Saliva substitutes [(e.g. Xialine, Oral Balance , Saliva Orthana , Salinum mouth rinses, Chlorhexidine mouth rinses); subjects will be required to withhold dosing 90 minutes prior to efficacy assessments.
- Oral muscarinic agonists (such as pilocarpine and cevimeline) provided subjects are on a stable regimen for at least 30 days prior to Day 0 and continue this dose for the duration of the study. Subjects will be required to withhold dosing with these agents in the 24h prior to all efficacy assessments.
- Anticholinergic agents, such as tricyclic antidepressants, bupropion, antihistamines, phenothiazines, antiparkinsonian drugs, anti-asthmatic medications, or gastrointestinal (GI) medications that cause xerostomia in more than 10% of patients, provided that a subject is on a stable regimen for at least 30 days prior to Day 0.

#### **6.9.2. Prohibited Medications and Non-Drug Therapies**

- Concomitant biologic treatments (see SRM for examples)
- Conventional systemic immunosuppressive treatments and DMARDs (such as methotrexate and azathioprine) (see SRM for examples)
- Pharmacological topical ophthalmic agents (e.g. NSAIDs, corticosteroids, cyclosporine, diquafosal) are excluded from use in the study.
- Non muscarinic secretagogues (e.g. Anetholtritone, Bromhexine3 N-acetylcystein) are excluded from use in the study.

## **7. STUDY ASSESSMENTS AND PROCEDURES**

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table, Section [7.1](#).

**7.1. Time and Events Table**

Study Day	Screening (up to 35 days prior to Day 0)	Day 0	7 ± 1 days	28 ± 7 days	56 ± 7 days	70 ± 7 days	84 ± 7 days	112 ± 7 days	140 ± 7 days	168 ± 7 days	196 ± 7 days	224 ± 7 days	252 ± 7 days	280 ± 7 days	308 ± 7 days	336 ± 7 days	364 ± 7 days	General follow up period <sup>1</sup>	Individualized follow up period (IFU) <sup>6</sup>	IFU Final Visit
Study Week	W -5		W1	W4	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W68		
Informed consent	X																			
Inclusion and exclusion criteria	X																			
Demography	X																			
Full physical exam	X	X <sup>3</sup>															X	X		X
Abbreviated physical exam symptom directed			X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Past & current medical conditions [including AECG criteria & CV medical history]	X																			
Urine pregnancy test (WCBP) in clinic <sup>9</sup>	X	X <sup>3</sup>		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X <sup>10</sup>	X <sup>3</sup>	X	X	X	X	X <sup>10</sup>	X	X	X <sup>10</sup>	X	X	X <sup>10</sup>	X	X	X	X <sup>10</sup>	X <sup>10</sup>	X	X <sup>10</sup>
Randomization		X																		
Belimumab/placebo.(weekly, home, except 1 <sup>st</sup> & 2 <sup>nd</sup> dose), last dose wk 51		X <sup>11</sup>	X <sup>11</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X				
Monitor in clinic after dosing for 3hrs (1 <sup>st</sup> & 2nd dose of belimumab/pbo)		X	X																	
Rituximab/placebo (at site)					X <sup>8</sup>	X <sup>8</sup>														
Monitor in clinic after dosing for 1h post rituximab/placebo					X	X														



Study Day	Screening (up to 35 days prior to Day 0)	Day 0	7 ± 1 days	28 ± 7 days	56 ± 7 days	70 ± 7 days	84 ± 7 days	112 ± 7 days	140 ± 7 days	168 ± 7 days	196 ± 7 days	224 ± 7 days	252 ± 7 days	280 ± 7 days	308 ± 7 days	336 ± 7 days	364 ± 7 days	General follow up period <sup>1</sup>	Individualized follow up period (IFU) <sup>6</sup>	IFU Final Visit
Study Week	W -5		W1	W4	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W68		
ESSDAI <sup>16</sup>	X						X			X			X				X	X		X
ESSPRI	X						X			X			X				X	X		X
Oral Dryness numerical resp. scale	X						X			X			X				X	X		X
Ocular Dryness numerical resp. scale	X						X			X			X				X	X		X
Salivary gland biopsy	X <sup>5</sup>									X <sup>12</sup>							X <sup>13</sup>			
Lacrimal function (Schirmer's) test	X						X			X			X				X			
Fatigue- (PROFAD SSI SF)	X									X			X				X			
Patient Global Assessment (PtGA)	X									X			X				X			
Physicians Global Assessment (PGA)	X									X			X				X			
Exit interview <sup>19</sup>																	X			
Stimulated Salivary Flow	X						X			X			X				X	X		X
Unstimulated Salivary Flow	X						X			X			X				X	X		X
Blood: Leukocyte population <sup>2</sup>	X	X <sup>3</sup>	X	X	X		X			X	X		X		X		X	X	X	X
Serological biomarkers	X	X <sup>3</sup>			X		X	X		X	X		X		X		X	X	X	X
Saliva sample for proteomics	X						X			X			X				X			
Blood: BLyS levels <sup>2</sup>		X <sup>3</sup>		X	X		X	X		X	X		X		X		X	X		X
Blood: Transcriptomics		X <sup>3</sup>			X					X			X				X			
Salivary gland: Transcriptomics	X									X							X <sup>13</sup>			
Blood: PBMC exploratory endpoints		X <sup>3</sup>			X					X										
Blood: Belimumab PK <sup>2</sup>										X			X		X		X			
Blood: Rituximab PK <sup>2</sup>					X <sup>7</sup>	X <sup>7</sup>	X			X			X							

Study Day	Screening (up to 35 days prior to Day 0)	Day 0	7 ± 1 days	28 ± 7 days	56 ± 7 days	70 ± 7 days	84 ± 7 days	112 ± 7 days	140 ± 7 days	168 ± 7 days	196 ± 7 days	224 ± 7 days	252 ± 7 days	280 ± 7 days	308 ± 7 days	336 ± 7 days	364 ± 7 days	General follow up period <sup>1</sup>	Individualized follow up period (IFU) <sup>6</sup>	IFU Final Visit
Study Week	W -5		W1	W4	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W68		
AE/SAE review	X <sup>17</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>18</sup>	X
Vital signs	X	X <sup>3,4</sup>	X <sup>4</sup>	X	X <sup>4</sup>	X <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X																			
CSSRS (suicidality assessment)		X <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Neurological assessment		X <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X <sup>3</sup>					X			X			X				X	X		X
Blood: Immunoglobulin levels (IgG, IgA <sup>2</sup> , IgM <sup>2</sup> )	X	X <sup>3</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood: Cryoglobulins	X						X			X			X				X	X		X
Blood chemistry	X	X <sup>3</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X <sup>3</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, Hep B and Hep C screen	X <sup>14</sup>																	X		
Pharmacogenetics blood sample <sup>15</sup>		X																		
Blood: Belimumab Immunogenicity <sup>2</sup>		X <sup>3</sup>			X					X							X	X		
Blood: Rituximab Immunogenicity <sup>2</sup>					X <sup>3</sup>					X							X			

**Footnotes:**

1. All subjects, including subjects who are withdrawn from the study (See Section 5.4.1) and decline to complete the treatment phase visits through Week 52, are required to enter the general follow up period. During this 16-week general follow up period, subjects will receive calls every 4 weeks (±7 days) to evaluate AEs, to check concomitant medications and to complete the neurological assessment (Appendix 5).
2. In order to maintain the blind, sites will be blinded to these data following screening - including B-cell flow cytometry panels and IgA, IgM levels.
3. To be measured or collected pre-dose.
4. Subjects will be monitored post study treatment as detailed in protocol.

5. Biopsy can occur on Day 0 or at any time during the screening period provided the subject has met all other entry criteria prior to the biopsy.
6. Subjects will enter the IFU if, following the general follow up period, their CD19+ B-cell levels remain below the lower limit of normal (or less than 90% of baseline, if baseline value was below LLN). During the IFU, subjects will be seen in the clinic every 12 weeks ( $\pm 7$  days), with calls every 4 weeks ( $\pm 7$  days) between visits to evaluate subjects for AEs & concomitant medications. Subjects will exit the IFU when: CD19+ B-lymphocyte counts are within normal range or 10% of baseline levels (if baseline < LLN), OR at the investigator's discretion the subject starts receiving disease modifying therapy that may affect B-cell numbers OR or for up to a maximum of 2 years (i.e., up to Week 104) – whichever comes first. Subjects exiting IFU period will attend a final visit (within 28 days of that decision) for final assessments (IFU Final Visit) as detailed in the Table.
7. Obtain samples post-dose only, within 10 minutes after end of infusion.
8. Both doses of rituximab/placebo will be administered in the clinic. Approximately 60 minutes prior to rituximab/placebo, subjects will receive orally an antipyretic and an antihistamine. At least 30 minutes prior to administration of rituximab/placebo, subjects will receive IV 100mg methylprednisilone. The 2nd rituximab/placebo administration at the Week 10 visit must be given 14 days (13-18 days, see SRM) after the first administration (given at the Week 8 visit). A patient alert card should be sent home with the subject following each dose of rituximab/placebo.
9. If urine test is positive, confirm with serum test. Pregnancy testing & contraception are required until 16 weeks post last administration of study treatment for those subjects who complete Weeks 46- 52 or withdraw from treatment prior to Week 8 dosing. Pregnancy testing and contraception are required for approximately 12 months after the administration of the final rituximab/placebo dose for the subset of subjects who discontinue treatment from Week 8 up to Week 46.
10. Subjects will receive a reminder phone call 48 hours prior to efficacy assessment visits to remind them that they should not be using certain symptomatic therapies prior to visit (see Section 4.1 of Study Reference Manual for details); in addition subjects should document their last use of symptomatic therapies in their self injection log book.
11. First & second dose of belimumab will be administered in clinic by subject or caregiver. A patient alert card will be sent home with the subject each time belimumab is dispensed for home administration.
12. Week 24 biopsy may be taken on a separate day from the other required assessments within the Week 24 study visit window.
13. Week 52 biopsy is optional. Transcriptomics will only be performed if biopsy is taken.
14. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
15. Informed consent for optional substudies e.g., genetics must be obtained before collecting a sample.
16. If additional tests (e.g., pulmonary function tests, EMG, MRI) are required to complete ESSDAI assessment, these should be scheduled as close as possible to the stipulated study visit window.
17. From signing of consent until initiation of study treatment, only SAEs related to study participation will be collected.
18. From the end of general follow-up phase through the last contact (including the individualized safety follow-up phase), only designated AESIs (i.e., infections, malignancies, and depression/suicidality/self-injury), fatal SAEs, and SAEs assessed as related to the investigational product or to study participation will be collected.

## 7.2. Screening and Critical Baseline Assessments

Information collected during the Screening Phase assessments described below represents key data that identifies and defines subject baseline status. This information is critical for the evaluation and comparison of subsequent safety and efficacy assessments.

**Informed Consent:** Informed consent will be obtained from the subject prior to the initiation of any study procedures or study-specific data collection.

Subjects who give written informed consent will enter a screening period of up to 35 days. A subject may be randomized when all screening procedures have been completed and eligibility criteria confirmed. During the screening period the following assessments will be performed:

**Demographic parameters** will be captured: year of birth, sex, race and ethnicity.

**Medical/medication/family history** will be assessed as related to the inclusion/exclusion criteria listed in Section 5. A complete medical history will be taken at the screening visit. Information from the medical history is important to establish the baseline condition of the subject, and will impact the safety monitoring assessments during the study. Any significant medical conditions affecting the subject in the past 5 years should be recorded on the Medical Conditions page of the eCRF. The history should include the following:

- Past or current conditions.
- Prior surgical procedures.
- Pharmacotherapy and chronic or recent use of any medication or herbal preparation.
- Prior immunosuppressive therapies, including type, number, and duration.
- Allergies and significant allergic reactions.
- Significant infections, or history of recurrent infection, including urinary and respiratory tract infections.
- Smoking history (current or previous smoker, number of cigarettes smoked per day).
- Cardiovascular medical history/risk factors (as detailed in the eCRF).

**Urine Pregnancy Test:** A test will be performed for women of child-bearing potential: monthly during the double blind treatment with investigational product (up to Week 52) and then at each clinic visit during the general and individualized follow up phases (see Time and Events Table in Section 7.1). Refer to the pregnancy section (Section 7.4.2).

**Full physical examination:** will include complete assessment of all organ systems including assessments of the head and neck (including eyes, ears, nose, throat, and thyroid gland), skin, musculoskeletal (including evaluation of both small and large joints), neurological, respiratory, and cardiovascular systems, gastrointestinal system and abdomen (including liver and spleen), lymph nodes and extremities.

**Electrocardiogram:** 12-lead ECGs will be obtained at screening. A single method (Bazett's or Fredericia's) must be used when calculating the corrected QT interval for determining subject eligibility, as described in the study reference manual (SRM).

**American European Consensus Group (AECG) criteria:** The 2002 American European Consensus Group criteria [Vitali, 2002] will be evaluated by the investigator to verify the subject's diagnosis of Primary Sjögren's Syndrome. The AECG criteria provide an assessment of six different parameters including: oral and ocular symptoms, oral and ocular signs, and objective measures of histopathology and biomarkers.

**Unstimulated and stimulated salivary flow:** Unstimulated and stimulated salivary flow rate will both be assessed as an entry criteria to ensure that subjects entered into the study have residual glandular function. Subjects with 0.0 mL/min unstimulated salivary flow rate may qualify for the study on the basis of stimulated salivary flow greater than 0.05 mL/min. Details of the collection procedure will be further specified in the SRM.

**Oral dryness Numerical Response Scale (NRS):** subjects are required to have symptomatic oral dryness as assessed by a score of at least 5 points on the 10 point NRS. The oral dryness NRS will be detailed in the SRM.

**ESSDAI:** subjects are required to have systemically active disease as determined by an ESSDAI score of at least 5 points. The ESSDAI [Seror, 2014] is an assessment of disease activity across twelve different clinically relevant domains for subjects with Sjögren's syndrome. ESSDAI will be assessed by the treating physician (preferably the same physician at each visit). Details and guidance regarding the application of the ESSDAI assessment will be provided in the SRM. A recent user's guide has also been published [Seror, 2015].

**Serological Biomarkers:** Quantification of serum analytes, autoantibodies [including anti-SS-A, SS-B], markers of B cells activation [may include but not limited to Beta-microglobulin, free kappa and lambda light chain], BLYS and other cytokines [may include but not limited to BLYS/Belimumab complex, IL-6, IL-21], chemokines [may include but not limited to CXCL13 and CCL19] and other analytes associated with immune activation or inflammation [may include but not limited to complement C3, C4, CH50, Cryoglobulin, CRP] or Sjögren's biology will be performed.

**Urinalysis:** will be performed as related to the eligibility criteria listed in Section 5.

**Blood immunoglobulin (IgG, IgA, IgM) screening:** will be performed as related to the eligibility criteria listed in Section 5.

**Tuberculosis:** Assessment of TB in the screening period is to be done via evaluation of the subject's history, physical examination of the subject and, if judged necessary by the Investigator, local laboratory testing. For subjects in Argentina only, the central lab will perform Quantiferon Gold testing.

**Hematology and blood chemistry (clinical safety laboratory assessments):** will be performed as related to the eligibility criteria listed in Section 5.

**HIV, Hepatitis B and C screening:** will be performed as related to the eligibility criteria listed in Section 5.

**Salivary gland biopsy:** The salivary gland biopsy surgical technique is described in the SRM. Training reference materials will be provided to site personnel who will perform this procedure.

Biopsy tissue will be shipped to a central histopathology laboratory for processing and assessment. The baseline biopsy can occur on Day 0 or at any time during the screening period provided the subject has met all other entry criteria prior. After the interim analysis, dependent on data, the biopsy may no longer be a mandatory requirement.

### 7.3. Efficacy

Planned time points for all efficacy assessments are listed in the Time and Events Table in Section 7.1. Time windows are provided for each study visit to allow flexibility in site and subject scheduling. All study visits should occur within the visit window of the scheduled study visit. Details regarding the execution of the efficacy assessments described below can be found in the SRM.

**ESSDAI:** The ESSDAI [Seror, 2014] is an assessment of disease activity across 12 different clinically relevant domains for subjects with Sjögren's syndrome. ESSDAI will be assessed by the treating physician (preferably the same physician at each visit). A recent user's guide has also been published [Seror, 2015].

**Un-stimulated and stimulated salivary flow:** Unstimulated salivary flow rate and stimulated salivary flow will be measured. Details of the collection procedure will be further specified in the SRM.

**Salivary gland biopsy:** The salivary gland biopsy surgical technique is described in the SRM. Training reference materials will be provided to site personnel who will perform this procedure.

Biopsy tissue will be shipped to a central histopathology laboratory for processing and assessment. After an interim analysis, dependent on data, the biopsy may no longer be a mandatory requirement.

**Schirmer's test:** is an assessment of lacrimal gland function in which a strip of filter paper is applied under the eyelid to measure the quantity of tear production. The technique for administration of this test will be described in the SRM.

**PGA:** the Physician's Global Assessment is a physician reported visual analogue scale that provides an overall measure of the subject's current disease activity. The assessment instrument and technique for administration will be described in the SRM.

**Oral dryness NRS:** A description of the anchors and directions for administering this scale will be provided in the SRM.

### 7.3.1. Patient-Reported Outcomes Assessments

Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

**ESSPRI:** the EULAR Sjögren's Syndrome Patient Reported Index [[Seror, 2014](#)] is an assessment of the severity of patients' symptoms in primary Sjögren's syndrome over the past 2 weeks, including dryness, pain (joint or muscular pains in arms or legs), and fatigue, on a 0-10 NRS for each symptom. The ESSPRI assessment tool will be detailed in the SRM..

**Oral and Ocular Dryness:** will be reported by subjects on a NRS from 0 to 10. The NRS will be translated into local languages. A description of the instrument anchors and technique for administering these scales will be described in the SRM.

**PROFAD-SSI-SF:** the Profile of Fatigue and Discomfort - Sicca Symptoms Inventory (Short Form) questionnaire is an assessment of fatigue, discomfort, and SICCA symptoms, on a 0-7 NRS for each item. Details will be provided in the SRM.

**PtGA:** the Patient Global Assessment is a patient reported numeric rating scale that provides an overall measure of disease severity. The assessment instrument and technique for administration will be described in the SRM.

**Exit Interviews:** Exit interviews will be conducted as shown in the Schedule of Events (Section 7.1) to explore subjects' experience with study treatment. Exit interviews are qualitative interviews conducted with study subjects to capture subject experiences in drug development on completion of participation in a clinical study. Interview questions designed to fully assess a subject's experience with a study medication are administered in a semi-structured format by a trained interviewer. Subject feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis. The Exit interview technique and questions will be described in the SRM and training as well as training material references will be provided to site personnel who will administer the Exit interviews.

## 7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table in Section 7.1. Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

### 7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in [Appendix 7](#).

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

**7.4.1.1. Time Period and Frequency for Collecting AE and SAE Information**

- AEs and SAEs will be collected from the start of Study Treatment through the general follow-up period (see Section 4.3 and the Time and Events Table in Section 7.1)
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- During the individualized safety follow-up phase (if applicable, see Section 4.3 and the Time and Events Table in Section 7.1), only SAEs assessed as related to the investigational product or to study participation, fatal SAEs, and designated AESIs (i.e., infections, malignancies, and depression/suicidality/self-injury) will be collected.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 7.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 7.

**7.4.1.2. Method of Detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

**7.4.1.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 7.4.1.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up



(as defined in Section 5.4.1). Further information on follow-up procedures is given in [Appendix 7](#).

#### **7.4.1.4. Adverse Events of Special Interest**

A number of adverse events of special interest have been identified as part of the risk assessment outlined in Section 4.7.1 due to the co-administration of two biologics and will be monitored for the duration of the study. These AESIs include infections (including opportunistic), systemic infusion / injection reactions, hypersensitivity reactions, malignancy, psychiatric events (including suicidality), severe skin reactions (including Toxic Epidermal Necrolysis and Stevens-Johnson syndrome), immunogenicity, cardiac disorders, posterior reversible encephalopathy syndrome (PRES), PML, and AE's related to the biopsy procedure. The analyses of these events will be described in the Reporting and Analysis Plan.

#### **7.4.1.5. Cardiovascular and Death Events**

For any cardiovascular events detailed in [Appendix 7](#) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

#### **7.4.1.6. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK of SAEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 7.4.2. Pregnancy

- Pregnancy testing and contraception are required until 16 weeks post last administration of study treatment for those subjects who complete Weeks 46-52 or withdraw from treatment prior to Week 8 dosing. Pregnancy testing and contraception are required for approximately 12 months after the administration of the final rituximab/placebo dose for the subset of subjects who discontinue treatment from Week 8 up to Week 46.
- Details of all pregnancies in female subjects will be collected for pregnancies occurring after the start of dosing and until either (a) 16 weeks post last administration of study treatment for those who complete Weeks 46-52 or withdraw from treatment prior to Week 8 dosing or (b) 12 months after the last administration of rituximab/placebo for subjects who discontinue treatment from Week 8 up to Week 46.
- If a pregnancy is reported, then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures as outlined in [Appendix 8](#).
- Women who become pregnant while on active treatment will be withdrawn from therapy but will continue in the trial for safety reporting and outcomes assessments. The pregnancy must be followed up to determine outcome (including premature termination), and status of mother and child including a one-year pediatric follow-up.

### 7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Head and Neck, Skin, Cardiovascular, Respiratory, Gastrointestinal, Musculoskeletal and Neurological systems. Height and weight will also be measured and recorded.
- An abbreviated physical examination will include, at a minimum, assessments of the eyes, mouth, skin, joints, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- A questionnaire-based neurological examination to detect any signs or symptoms consistent with the diagnosis of PML will be conducted at each visit. The questionnaire is shown in [Appendix 5](#). If any question is answered 'yes' and the reason for the symptom is unknown (i.e., is not definitively explained by other known cause), the subject will be referred to a neurologist for evaluation. An MRI with gadolinium enhancement (pending renal function evaluation) and/or Cerebrospinal Fluid (CSF) JCV PCR are recommended to be performed to confirm the diagnosis. In addition, the investigator should contact the Medical Monitor within 2 business days if any question is answered 'yes,' regardless of suspected cause, to discuss appropriate management of the patient. Any findings should be reported as an adverse event and the PML reporting procedures followed, as in Section [7.4.7](#). A PML Adjudication Committee will review all cases of PML and suspected PML, and will provide their opinion to the sponsor.

#### **7.4.4. Vital Signs**

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken.
- First reading should be rejected.
- Second and third readings should be averaged to give the measurement to be recorded in the eCRF.

#### **7.4.5. Electrocardiogram (ECG)**

- 12-lead ECGs will be obtained at screening. If the ECG demonstrates a QTcB or QTcF interval  $\geq 450$  msec ( $\geq 480$  msec for subjects with a Bundle Branch Block), there is a requirement to obtain two additional, consecutive ECGs (for a total of three). The investigator will then average the three QTc (and QT) intervals obtained and document the following from the 1st ECG:
  - Rate
  - PR interval
  - QRS axis

#### **7.4.6. Clinical Safety Laboratory Assessments**

All protocol required laboratory assessments, as defined in the Time and Events Table (in Section 7.1) must be conducted in accordance with the Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and will be detailed in the SRM or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional, non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE) the results must be recorded in the eCRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used

to make either a treatment or response evaluation, the results must be entered into the eCRF.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in [Table 1](#).

**Table 1 Protocol Required Safety Laboratory Assessments**

Laboratory Assessments	Parameters			
Hematology	<u>CBC:</u>		<u>RBC Indices:</u>	<u>WBC Differential:</u>
	WBC Count		RBC Count	Neutrophils
	Hemoglobin		MCV	Lymphocytes
	Hematocrit		MCH	Monocytes
	Platelet Count			Eosinophils
				Basophils
Clinical Chemistry	Sodium	Chloride	BUN	Glucose
	Potassium	Bicarbonate	Creatinine	Calcium
	Total and direct bilirubin	ALT (SGPT)	AST (SGOT)	Alkaline phosphatase
	Total Protein	Albumin	Creatine Kinase	Uric acid
Routine Urinalysis	<ul style="list-style-type: none"><li>Specific gravity</li><li>pH, glucose, protein, blood and ketones by dipstick<ul style="list-style-type: none"><li>Microscopic examination (if blood observed or protein is abnormal)</li><li>Urine protein quantitative analysis (if indicated)</li></ul></li></ul>			
Additional safety tests	<ul style="list-style-type: none"><li>IgG, IgM, IgA.</li><li>CD19 B cell counts, CD4 &amp; CD8 cell counts</li></ul>			
Other Screening Tests	<ul style="list-style-type: none"><li>HIV, Hepatitis B (HBsAg) and HbcAb</li><li>Hepatitis C (Hep C antibody)</li><li>FSH and estradiol (as needed in women of non-child bearing potential only)</li><li>Serum or urine hCG Pregnancy test (as needed for women of child bearing potential)<sup>2</sup></li></ul>			
NOTES: Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.5 and Appendix 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.				

With the exception of CD19+ B-cell levels (see “Follow up period” in Section [4.3](#)), all laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

#### 7.4.7. Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating infection of the CNS caused by initial infection or reactivation of the John Cunningham virus (JCV). Asymptomatic primary infection with JCV typically occurs in childhood with latent virus remaining dormant in the kidneys and lymphoid organs. In the context of immunosuppression, the virus can reactivate and involve the brain. Prior to 2000, most cases of PML had a fatal outcome. PML has been recently associated with immunosuppressive therapy, notably natalizumab, rituximab, efalizumab, mycophenolate mofetil, and tacrolimus [Schmedt, 2012].

In order to accommodate potential development of PML, neurological examinations will be conducted at the time points indicated in Section 7.1, the Time and Events Table.

Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.

If a subject develops neurological signs or symptoms consistent with PML, treatment with investigational product should be halted and the subject referred to a neurologist or PML specialist for evaluation. Neurological evaluation for PML should focus on clinical symptoms, imaging studies and evidence of the virus in the CSF. The PML algorithm should be followed for all suspected cases of PML (See Appendix 4).

If the assessments are positive, the patient should proceed to the Follow-Up Period. All such patients will be followed until resolution. Any patient with a diagnosis of PML will be withdrawn from IP.

An independent PML Adjudication Committee will be utilized in this study to confirm any PML events. The PML Adjudication Committee will review blinded data for any subject with suspected PML and report the outcome of their adjudication review to the sponsor.

Note: The GSK Medical Monitor must be informed **within 2 business days** in the event a subject is identified as having neurological signs and symptoms suggestive of a diagnosis of PML. If PML is not confirmed, the investigator will inform the Medical Monitor of the relevant diagnosis and any action taken.

Refer to the SRM for further information and detailed guidance for completing and transmitting these and other SAE reports for patients who experience a serious infection, malignancy, death, sign or symptom of PML.

The investigator will do the following when reporting a serious infection (including PML) or sign/symptom consistent with PML.

Promptly report the event, as with any other SAE, as per Section 7.4.1.

Provide key source documentation for the Sponsor to assist with the safety evaluation process.

Examples of key source documents include but are not limited to: hospitalization records, discharge summaries, laboratory evaluations, biopsy results, culture/sensitivity results, death certificates, and autopsy reports.

If the patient has not otherwise been withdrawn from the study, then the investigator should contact the Sponsor to discuss the appropriate course of action regarding study continuation.

#### **7.4.8. Suicidal Risk Monitoring**

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. In this study, the Columbia Suicidality Severity Rating Scale (C-SSRS ( www.cssrs.columbia.edu) will be used to assess suicidal ideation and behavior. It is recommended that the Investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior. The Medical Monitor should be notified when these events occur. In addition, a “yes” to any suicidal behavior or ideation question on the C-SSRS prompts the completion of the Possible Suicidality Related Adverse Event Questionnaire (PSRAE) Details of the C-SSRS and PSRAE questionnaires will be provided in the SRM.

#### **7.5. Pharmacokinetics**

All randomized subjects will be sampled for serum belimumab and rituximab levels. Assessment of belimumab and rituximab concentrations will be performed at the time points indicated in Section 7.1, Time and Events Table. Details of blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

#### **7.6. Biomarker(s)/Pharmacodynamic Markers**

Samples for biomarkers and pharmacodynamic markers will be collected as indicated in Section 7.1, Time and Events Table.

The timing of collections may be adjusted based on emerging PK or PD data from this study or other information in order to ensure optimal evaluation of the PD endpoint.

Details of blood sample collection (including volume to be collected), processing, and storage will be provided in the SRM.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

### **7.6.1. Novel Biomarkers**

A secondary endpoint will be the quantification of B cells, such as a change in B/T cell ratio measured by immunohistochemistry (IHC) analysis of B and T cell numbers within lymphoid foci in the salivary gland as assessed at Day 0 and Week 24 and as described in Section 7.6.1.1.

An exploratory endpoint is to identify other mechanistic measures that may be more sensitive in detecting the effects of, or may provide more insight into, the effect of the co-administration treatment on the immune system and is described in Section 7.6.1.1 through Section 7.6.1.4. For all Biomarkers/PD assays and procedures, further details are provided in the SRM. Details of the analyses performed can be found in the RAP.

#### **7.6.1.1. Assessment of the Salivary Gland Cellular Composition**

Histological analysis of biopsy samples will include assessment of lymphocyte infiltrate, B cell and T cell subsets assessed through analysis of foci scoring, and IHC. IHC assessments may include B cell markers: CD20, IgG, IgM, IgA and CD38; T cell markers: CD3, markers of germinal center formation, CD21 and markers of dividing cells, Ki67. Changes in lymphocytes populations in glandular tissue may be further evaluated using epigenetic quantification or other equivalent technology and/or additional IHC markers of leukocyte infiltration and activation and/or glandular biology. Sections of salivary gland will be assessed by a pathologist to score glandular pathology.

#### **7.6.1.2. Peripheral Blood Leukocyte Analysis**

B cell flow cytometry panels will be used to measure changes over the course of therapy in the transitional, naive, memory and plasma B cell compartments. For subsets of interest, absolute numbers of cells and proportions relative to all B cells will be determined as well as activation status.

Peripheral blood mononuclear cells (PBMCs) may be collected and stored to allow for further evaluation of leukocyte populations to further support mechanistic understanding of treatment.

#### **7.6.1.3. Serological Biomarkers**

The quantification of serum analytes, autoantibodies [including anti-SSA and SSB], markers of B cells activation [may include but not limited to Beta-microglobulin, free kappa and lambda light chain], cytokines [may include but not limited to BLyS, IL-6, IL-21], chemokines [may include but not limited to CXCL13 and CCL19] and other analytes associated with immune activation [may include but not limited to complement C3, C4, and CH50] or Sjögren's biology will be performed using Luminex, ELISA or other appropriate technologies on serum or other assay appropriate blood matrix. Serum may be further analyzed for novel biomarkers and correlation with transcriptomic analysis of blood and glandular tissue. Serum for longitudinal analysis will be collected and stored for analysis at the end of the study.



#### **7.6.1.4. Additional Exploratory Biomarkers**

##### **7.6.1.4.1. Saliva Proteomics**

Saliva may be analyzed for novel biomarkers and correlation with transcriptomic and serologic analysis of blood and glandular tissue. Saliva for longitudinal analysis will be collected and stored as described in the SRM and may be analyzed at the end of the study.

##### **7.6.1.4.2. Transcriptomic Analysis**

Transcriptome studies on blood and salivary gland tissue may be conducted using microarray and/or alternative equivalent technologies including RNA sequencing (RNA-seq), which facilitates the simultaneous measurement of the relative abundance of thousands of RNA species, resulting in a transcriptomic profile for each blood and glandular sample. This will enable the evaluation of the changes in transcripts relevant to leukocyte activation, cellular composition and ectopic lymphoid structure development.

##### **7.6.1.4.3. B and T Cell Receptor Clonal Analysis**

An additional analysis of the effect of treatment on B and T antigen receptor clonal usage may be performed to assess the degree of expansion of B and T subpopulations in the blood and salivary gland tissue and the effect of treatment on expanded populations.

##### **7.6.1.5. Immunogenicity**

Serum samples will be collected for belimumab and rituximab immunogenicity assessment prior to dosing and after treatment start as indicated in Section 7.1, Time and Events Table.

#### **7.7. Genetics**

Information regarding genetic research is included in [Appendix 6](#).

### **8. DATA MANAGEMENT**

For this study, subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.



## **9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES**

### **9.1. Hypotheses and Treatment Comparisons**

The primary objective of the study is to investigate the safety and tolerability of the co-administration of belimumab with rituximab and belimumab monotherapy. No formal statistical comparisons will be conducted to assess this objective.

Secondary efficacy and mechanistic endpoints will be investigated. The following exploratory comparisons may be conducted:

- Co-administration belimumab/rituximab treatment arm vs. Placebo arm
- Co-administration belimumab/rituximab treatment arm vs. Rituximab monotherapy arm
- Co-administration belimumab/rituximab treatment arm vs. Belimumab monotherapy arm
- Belimumab monotherapy arm vs. Placebo arm
- Belimumab monotherapy arm vs. Rituximab monotherapy arm

If deemed appropriate, these exploratory comparisons will be made investigating ESSDAI, stimulated salivary flow, oral dryness numeric response scale and a subset of salivary gland and plasma B cell parameters. Full details will be included in the RAP.

For all other parameters, no formal statistical comparisons will be made, although trends over time will be investigated across all treatment arms.

### **9.2. Sample Size Considerations**

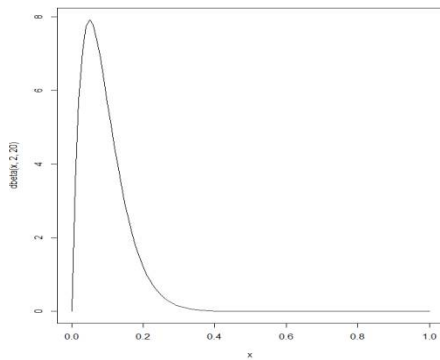
#### **9.2.1. Sample Size Assumptions**

The study is not powered to detect pre-defined differences. Initially, approximately 70 subjects will be recruited.

Following interim analysis the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 total subjects in the study where up to a maximum of 25, 45, 30 and 20 will be randomized to placebo, belimumab monotherapy, co-administration therapy and rituximab monotherapy, respectively. This will be dependent on variability and placebo rates for certain parameters. More details will be included in the RAP.

The primary objective of the study is safety, where a number of safety events are of interest. Using a Bayesian approach to determine the confidence interval around an observed safety event in the co-administration group, we would have a flat Beta(1,1)

prior, and if we were to observe 1 safety event in 20 then the posterior distribution would be Beta (2,20), as outlined below:



We can be 95% certain that the true probability of the safety event lies between 0.01 and 0.24.

For supportive information, with 20 patients randomized to belimumab or the belimumab / rituximab arm and 10 to placebo, the smallest difference in ESSDAI between the two treatment groups that would be statistically significant would be -3.30, assuming a placebo change from baseline of -1.7 [TEARS, [Devauchelle-Pensec, 2014](#)], a standard deviation of 4.192 [BELISS, [Mariette, 2015](#)] and alpha=5%.

Following the interim analysis, if the number of subjects were to increase to those outlined above then the following would apply for the continuous ESSDAI score, assuming a placebo change from baseline of -1.7 [TEARS, [Devauchelle-Pensec, 2014](#)], a standard deviation of 4.192 [BELISS, [Mariette, 2015](#)] and alpha=5%:

Placebo	Active	Difference	Placebo N	Active N	Power to detect difference
-1.7	-4.7	3	25	45	82%
-1.7	-4.7	3	25	40	80%
-1.7	-4.7	3	25	35	78%
-1.7	-4.7	3	25	30	75%

For responder endpoints, including the proportion of patients who achieve a 30% improvement in oral dryness response scale; or the proportion of patients who achieve a 30% improvement in stimulated salivary flow, then the smallest difference between the 2 treatment groups that would be statistically significant is 33%, assuming a placebo response of 14%, for example.

Twenty subjects randomized to the rituximab arm, would enable a reasonable evaluation of the impact of treatment on the underlying immunological mechanisms but not the clinical efficacy.

### 9.2.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of subjects who completed the 24 weeks is lower than 20 in the co-administration group, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in the table below:

N completing study	Number of particular safety events observed with co-administration	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
18	0 / 18	18%
18	1 / 18	26%
16	0 / 16	20%
16	1 / 16	29%
14	0 / 14	22%
14	1 / 14	32%

### 9.2.3. Sample Size Re-estimation

At the interim analysis, the sample size may be re-estimated based on the emerging data from the study. The sample size may need to be re-estimated if higher variability or differing placebo means are observed for the ESSDAI, a key secondary endpoint. Therefore, any significant deviation from the assumptions used to design the study may result in changes to the number of subjects to be randomized. Further details will be included in the RAP and guidance document for interim decision making. A maximum of 120 subjects will be recruited into the study.

## 9.3. Data Analysis Considerations

### 9.3.1. Analysis Populations

**Safety Population:** The ‘Safety Population’ is defined as subjects who receive at least one dose of study medication. This population is used for the summary of all data including safety efficacy and pharmacodynamic (PD) data but excluding PK data.

**Pharmacokinetic Population:** The ‘PK Population’ is defined as subjects in the ‘Safety’ population who received an active dose and for whom a pharmacokinetic sample was obtained and analyzed. This population is used for the summary of PK data only. In the case of PK/PD, the Safety Population is used so that subjects receiving placebo can be included.

### 9.3.2. Interim Analysis

In line with routine pharmacovigilance, subjects’ blinded safety data will be reviewed on an ongoing basis during the study conduct by an internal GSK Safety Review Team (SRT).

An internal GSK Safety Review Committee (iSRC), independent of the study team, will maintain governance of the study and will periodically review all available data in an un-blinded manner with a focus on key safety parameters. A Therapeutic Area (Immuno-Inflammation) Data Assessment Committee (TA DAC), independent of the study team, will periodically review un-blinded efficacy data and at the interim analysis will advise the iSRC on adaptive design changes should such changes be required. An iSRC charter details the activities of these committees, including when and which data will be reviewed, how the integrity of the study will be maintained, and the membership of both committees. Once half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, on an exploratory basis, preliminary efficacy analysis may be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be mandated by the iSRC: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.

#### **9.4. Key Elements of Analysis Plan**

##### **9.4.1. Primary Analysis and Follow Up Analysis**

In addition to the interim analysis, there will be additional analyses for this study, corresponding to the primary analysis and the follow-up analyses. The primary analysis will occur after the data through the Week 52 visit (or withdrawal visit for those subjects who withdraw during double-blind treatment) for all subjects has been collected, verified and validated. The follow up analyses will occur after data through the 16-week generalized follow-up period and IFU periods for all subjects has been collected, verified and validated. All subjects and study site personnel (except the unblinded site pharmacist) will remain blinded until the follow up analyses have been completed.

##### **9.4.2. Analysis of Primary Endpoints**

No formal statistical testing will be performed on safety data.

All safety evaluations will be based on the safety population. Clinical interpretation will be based upon review and displays of AEs, laboratory values and vital signs. The principle consideration in this evaluation will be the investigator-reported relationships of either AEs or laboratory abnormalities to IP.

Safety data will be presented in tabular and/or graphical format.

##### **9.4.3. Analysis of Secondary Endpoints**

All data will be descriptively summarized, graphically presented and listed appropriately.

Each endpoint will be considered individually and at the treatment level where comparisons between treatment groups would be made on any changes observed.

The relationship between the mechanistic (e.g., salivary gland B cell quantification) and clinical effects (e.g., ESSDAI score) will be graphically presented. The consistency in the changes over time between the endpoints will be assessed and further exploratory analyses to characterise relationships between endpoints may be conducted.

The ESSDAI, stimulated salivary flow and oral dryness numeric response scale change from baseline scores will be statistically analyzed using a mixed model repeated measures approach. Point estimates and corresponding 95% confidence intervals will be estimated for all the comparisons of interest (see Section 9.1) at weeks 24 and 52. Distributional assumptions underlying the analyses will be assessed. Additional models may be investigated.

Non-parametric statistical analyses will also be conducted to assess the comparisons of interest for a subset of salivary gland histology assessments, and B cell quantification in plasma. These analyses will be described in the RAP.

In addition, based on the data that we observe in the study, probabilities of success of the co-administration therapy and belimumab monotherapy may be determined. For example, what is the probability that we would observe a certain change in the ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

Further details regarding the statistical analysis will be outlined in the RAP.

#### **9.4.4. Analysis of Other Endpoints**

##### **9.4.4.1. Health Outcome Analyses**

Pain, dryness, and fatigue will be assessed over time using the ESSPRI total score and subscale scores. In addition, the PROFAD-SSI-SF will assess fatigue, discomfort and sicca symptoms. The PtGA and PGA will be performed to assess disease activity. At the end of the study, patients will participate in an exit interview where they will be asked to report on their experience with treatment during the clinical trial. Questions will be asked regarding treatment benefit, side effects, and study design (in terms of patient burden). The interview data will be qualitatively analyzed and will serve to inform expected magnitude of treatment benefit, risk tolerance, and future study design considerations.

All health outcome measures will be listed, summarized and presented graphically over time where appropriate. Further details will be included in the RAP.

##### **9.4.4.2. Pharmacokinetic Analyses**

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

#### **9.4.4.3. Pharmacokinetics/Pharmacodynamic Analyses**

The relationship between B-cells and belimumab concentrations will be explored graphically. A PK/PD modeling approach may be used to quantify the relationship.

More details of any exploratory pharmacokinetic/pharmacodynamic analyses will be provided in the RAP.

### **10. STUDY GOVERNANCE CONSIDERATIONS**

#### **10.1. Posting of Information on Publicly Available Clinical Trial Registers**

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

#### **10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

Prior to initiation of a site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments, as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- Regulatory Agency review and favorable opinion/approval of the study protocol and substantial amendments.
- GSK will provide full details of the above procedures, either verbally, in writing, or both
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.

- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

### **10.3. Quality Control (Study Monitoring)**

In accordance with applicable regulations including GCP and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

### **10.4. Quality Assurance**

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

### **10.5. Study and Site Closure**

Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures. GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action. If the study is

suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## **10.6. Records Retention**

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions. GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements. The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

## **10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis. The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy. A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.



## **10.8. Review Committees**

### **10.8.1. Internal Safety Review Committee (iSRC) and Therapeutic Area Data Assessment Committee (TA-DAC)**

An internal GSK Safety Review Committee (iSRC), independent of the study team, will maintain governance of the study and will periodically review all available data in an un-blinded manner with a focus on key safety parameters. A Therapeutic Area (Immuno-Inflammation) Data Assessment Committee (TA DAC), independent of the study team, will periodically review un-blinded efficacy data and at the interim analysis will advise the iSRC on adaptive design changes should such changes be required. An iSRC charter details the activities of these committees, including when and which data will be reviewed, how the integrity of the study will be maintained, and the membership of both committees.

The overall responsibility of the iSRC is to protect the ethical and safety interests of subjects recruited into the study while also protecting the scientific validity of the data. The iSRC has the primary governance role for the study.

### **10.8.2. PML Adjudication Committee**

An independent PML Adjudication Committee will be utilized in this study to confirm any PML events. The PML Adjudication Committee will review blinded data for any subject with suspected PML and report the outcome of their adjudication review to the sponsor.

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## 12. APPENDICES

### 12.1. Appendix 1: Abbreviations and Trademarks

#### Abbreviations

ADA	Anti-drug antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	Adverse Event
AECG	American European Consensus Group
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the Curve
BLyS	B lymphocyte stimulator
CBC	Complete Blood Count
CMM	Cubic Millimeter
CNS	Central Nervous System
CRP	C-Reactive Protein
C-SSRS	Columbia Suicidality Severity Rating Scale
CV	Cardiovascular
eCRF	Electronic Case Report Form
CSF	Cerebrospinal Fluid
DMARD	Disease-modifying anti-rheumatic drugs
ECG	Electrocardiogram
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
DILI	Drug Induced Liver Injury
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FRP	Females of Reproductive Potential
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HSR	Hypersensitivity reactions
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry

INN	International Nonproprietary Name
IP	Investigational Product
IRB	Institutional Review Board
iSRC	Internal Safety Review Committee
IVIG	Intravenous Immunoglobulin
JCV PCR	John Cunningham virus polymerase chain reaction test
LLN	Lower Limit of Normal
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MMRM	Mixed Effect Model Repeat Measurement
MRI	Magnetic Resonance Imaging
NRS	Numerical Response Scale
NSAID	Non steroidal anti-inflammatory drug
OI	Opportunistic Infection
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PGA	Physicians Global Assessment
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PNS	Peripheral Nervous System
PRES	Posterior Reversible Encephalopathy Syndrome
PROFAD-SSI-SF	Profile of Fatigue and Discomfort Sicca Symptoms Inventory Short Form
PSRAE	Possible Suicidality Related Adverse Event Questionnaire
pSS	Primary Sjögren's Syndrome
PtGA	Patient Global Assessment of Disease Activity
QD	Once a day
R&D	Research and Development
RAMOS NG	Randomization and Medication Ordering System Next Generation
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RF	Rheumatoid Factor
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Event
SLE	Systemic Lupus Erythematosus
SRM	Study Reference Manual
SRT	Safety Review Team
SS-A	Anti-Sjögren's-syndrome-related antigen A
SS-B	Anti-Sjögren's-syndrome-related antigen B
TA-DAC	Therapeutic Area – Data Assessment Committee
TB	Tuberculosis
ULN	Upper Limit of Normal
USAN	United States Adopted Names
WBC	White Blood Cell

**Trademark Information**

<b>Trademarks of the GlaxoSmithKline group of companies</b>
BENLYSTA

<b>Trademarks not owned by the GlaxoSmithKline group of companies</b>
Chiron RIBA
Luminex
MabThera
Rituxan
SAS
WinNonlin

## 12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

**Phase II 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).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

### Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
<b>ALT-absolute</b>	ALT $\geq$ 5xULN
<b>ALT Increase</b>	ALT $\geq$ 3xULN persists for $\geq$ 4 weeks
<b>Bilirubin<sup>1, 2</sup></b>	ALT $\geq$ 3xULN <b>and</b> bilirubin $\geq$ 2xULN (>35% direct bilirubin)
<b>INR<sup>2</sup></b>	ALT $\geq$ 3xULN <b>and</b> INR>1.5, if INR measured
<b>Cannot Monitor</b>	ALT $\geq$ 3xULN and cannot be monitored weekly for 4 weeks
<b>Symptomatic<sup>3</sup></b>	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study treatment</li> <li>• Report the event to GSK <b>within 24 hours</b></li> <li>• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE<sup>2</sup></li> <li>• Perform liver event follow up assessments</li> <li>• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> <li>• <b>Do not restart/rechallenge</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is</b> granted (refer to <a href="#">Appendix 3</a>)</li> <li>• If restart/rechallenge <b>not allowed per protocol or not granted</b>, permanently discontinue study</li> </ul>	<ul style="list-style-type: none"> <li>• Viral hepatitis serology<sup>4</sup></li> <li>• Blood sample for pharmacokinetic (PK) analysis, obtained 6 weeks after last dose<sup>5</sup></li> <li>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>• Fractionate bilirubin, if total bilirubin<math>\geq</math>2xULN</li> <li>• Obtain complete blood count with differential to assess eosinophilia</li> <li>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</li> <li>• Record use of concomitant medications on the concomitant medications report</li> </ul>



<p>treatment and may continue subject in the study for any protocol specified follow up assessments</p> <p><b>MONITORING:</b></p> <p><b><u>For bilirubin or INR criteria:</u></b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24 hrs</b></li> <li>Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>For All other criteria:</u></b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24-72 hrs</b></li> <li>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</li> </ul>	<p>form including acetaminophen, herbal remedies, other over the counter medications.</p> <ul style="list-style-type: none"> <li>Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>For bilirubin or INR criteria:</u></b></p> <ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).</li> <li>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]). <b>NOTE: not required in China</b></li> <li>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.</li> </ul>
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1. 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  $\geq$  3xULN and bilirubin  $\geq$  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.
2. All events of ALT  $\geq$  3xULN and bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  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
3. 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)
4. 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
5. 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.

**Phase II liver chemistry increased monitoring criteria with continued therapy**

<b>Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event</b>	
<b>Criteria</b>	<b>Actions</b>
ALT $\geq$ 3xULN and <5xULN <b>and</b> bilirubin <2xULN, <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 4 weeks	<ul style="list-style-type: none"><li>• Notify the GSK medical monitor <b>within 24 hours</b> of learning of the abnormality to discuss subject safety.</li><li>• Subject can continue study treatment</li><li>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline</li><li>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above</li><li>• If, after 4 weeks of monitoring, ALT &lt;3xULN and bilirubin &lt;2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</li></ul>

**References**

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

### 12.3. Appendix 3: Liver Safety – Study Treatment Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

#### ***Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment***

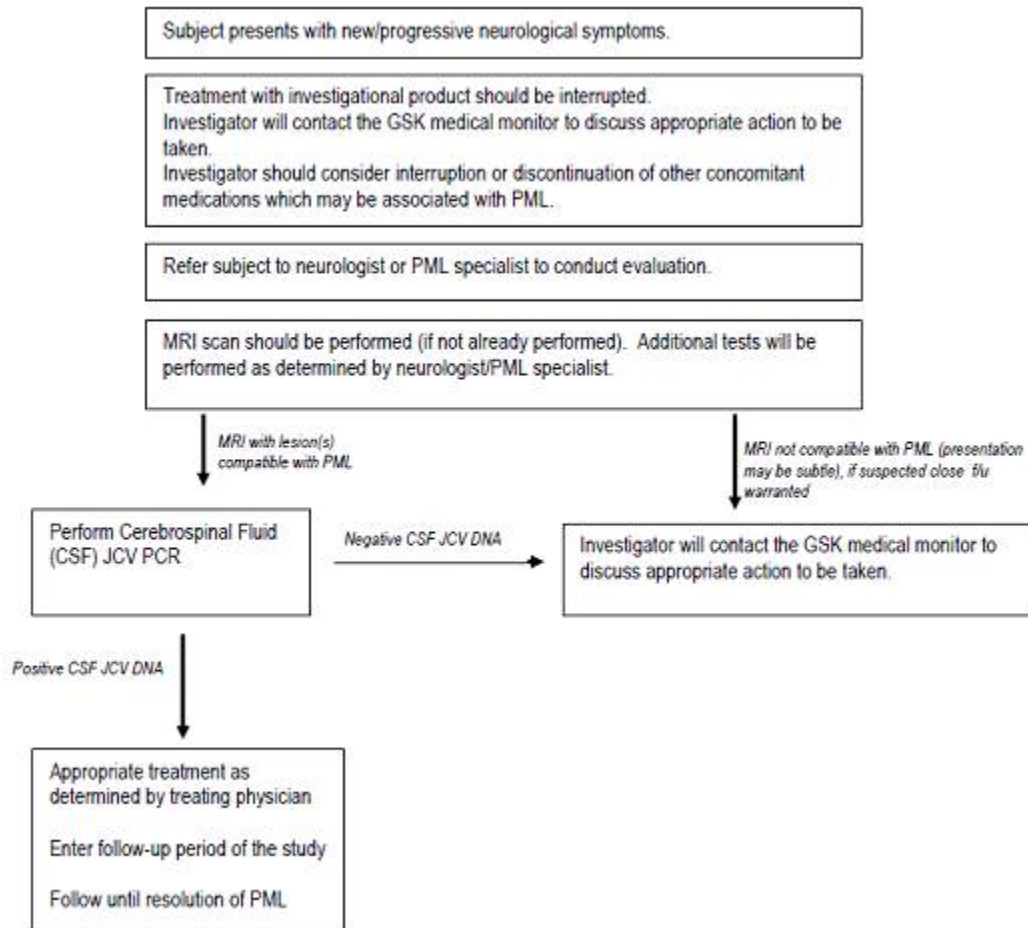
Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section [7.4.1.1](#).

## 12.4. Appendix 4: PML Algorithm



**12.5. Appendix 5: Neurological Symptoms Questionnaire**

	YES	NO
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.		

If any of the above are answered “Yes” at any visit, the investigator will contact the medical monitor.

Any neurological symptom that cannot be attributed to a concurrent medical condition or concomitant medication must be referred to a neurologist.

## 12.6. Appendix 6: Genetic Research

### Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including belimumab, ritixumab or any concomitant medicines;
- Sjögren's syndrome susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

### Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

### Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labeled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the

subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

### **Informed Consent**

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

### **Subject Withdrawal from Study**

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.



**Screen and Baseline Failures**

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance, a sample destruction form will not be available to include in the site files.

**Provision of Study Results and Confidentiality of Subject's Genetic Data**

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

## 12.7. Appendix 7: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

### 12.7.1. Definition of Adverse Events

#### Adverse Event Definition:

- An AE is 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.

#### Events meeting AE definition include:

- 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 judgement of the investigator.
- 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).
- "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 fulfil the definition of an AE or SAE.

#### Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- 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.

- 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.

### 12.7.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

**Serious Adverse Event (SAE) is defined as 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 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.
- 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**

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

<ul style="list-style-type: none"> <li>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</li> </ul>
<b>e. Is a congenital anomaly/birth defect</b>
<b>f. Other situations:</b> <ul style="list-style-type: none"> <li>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.</li> <li>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</li> </ul>
<b>g. Is associated with liver injury <u>and</u> impaired liver function defined as:</b> <ul style="list-style-type: none"> <li>ALT <math>\geq</math> 3xULN and total bilirubin* <math>\geq</math> 2xULN (&gt;35% direct), <b>or</b></li> <li>ALT <math>\geq</math> 3xULN and INR** <math>&gt;</math> 1.5.</li> </ul> <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT <math>\geq</math> 3xULN and total bilirubin <math>\geq</math> 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>

### 12.7.3. Definition of Cardiovascular Events

<b>Cardiovascular Events (CV) Definition:</b>
<p>Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:</p> <ul style="list-style-type: none"> <li>Myocardial infarction/unstable angina</li> <li>Congestive heart failure</li> <li>Arrhythmias</li> <li>Valvulopathy</li> <li>Pulmonary hypertension</li> <li>Cerebrovascular events/stroke and transient ischemic attack</li> </ul>

- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

#### 12.7.4. Recording of AEs and SAEs

##### **AEs and SAE Recording:**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed patient reported outcome questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the patient reported outcome questionnaires will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

#### 12.7.5. Evaluating AEs and SAEs

##### **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

**12.7.6. Reporting of SAEs to GSK****SAE reporting to GSK via InForm**

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or designee.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or designee by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

## **12.8. Appendix 8: Collection of Pregnancy Information**

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed for 1 year to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK..
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in this appendix. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

### **Any female subject who becomes pregnant while participating**

- will be withdrawn from therapy but will continue in the trial for safety reporting and outcomes assessments.



## 12.9. Appendix 9: American-European Consensus Group Classification

**Table 2** Revised international classification criteria for Sjögren's syndrome

- I. Ocular symptoms: a positive response to at least one of the following questions:
  1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
  2. Do you have a recurrent sensation of sand or gravel in the eyes?
  3. Do you use tear substitutes more than 3 times a day?
- II. Oral symptoms: a positive response to at least one of the following questions:
  1. Have you had a daily feeling of dry mouth for more than 3 months?
  2. Have you had recurrently or persistently swollen salivary glands as an adult?
  3. Do you frequently drink liquids to aid in swallowing dry food?
- III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
  1. Schirmer's I test, performed without anaesthesia ( $\leq 5$  mm in 5 minutes)
  2. Rose bengal score or other ocular dye score ( $\geq 4$  according to van Bijsterveld's scoring system)
- IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue<sup>18</sup>
- V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
  1. Unstimulated whole salivary flow ( $\leq 1.5$  ml in 15 minutes)
  2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts<sup>19</sup>
  3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer<sup>20</sup>
- VI. Autoantibodies: presence in the serum of the following autoantibodies:
  1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

**Table 3** Revised rules for classification

- For primary SS*  
 In patients without any potentially associated disease, primary SS may be defined as follows:
- a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
  - b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
  - c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey
- For secondary SS*  
 In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS
- Exclusion criteria:*  
 Past head and neck radiation treatment  
 Hepatitis C infection  
 Acquired immunodeficiency disease (AIDS)  
 Pre-existing lymphoma  
 Sarcoidosis  
 Graft versus host disease  
 Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

## References

Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis.* 2002; 61:554–8.

## 12.10. Appendix 10: Protocol changes in Amendment 1

### Amendment 1: Specific amendment for Sweden (all sites)

**Protocol Amendment 01, 15 October 2015**

#### Summary of Modifications (relative to original protocol) and Rationale:

1. Section 5.1 (Inclusion Criteria). This section has been updated to amend the list of acceptable methods of contraception.
2. Section 5.4 (Withdrawal/Stopping Criteria). The detailed Adverse Event Criteria (within Section 5.4.2) have been clarified to confirm that subjects will be withdrawn from investigational products in the event of a life- threatening infection.
3. Section 6.9.1 (Permitted Medications and Non-Drug Therapies). Correction of typographical error regarding the permitted dose of hydroxychloroquine.
4. Section 1 (Synopsis), Section 4.1 (Overall Design) and Section 9.3.2 (Interim Analysis). These sections have been updated to clarify both the timing and number of interim analyses.
5. Section 10.2 (Regulatory and Ethical Considerations, Including the Informed Consent Process). Updated to clarify that regulatory agency approval is required for the protocol AND for substantial amendments to the protocol.
6. Appendix 9 has been added to protocol and contains the American European Group Consensus Criteria for Primary Sjögren's Syndrome.

#### Associated Protocol Modifications:

##### Protocol Cover Page

*Add:*

Protocol Amendment Number: 1

*Updated:*

##### Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1
Protocol amended in response to comments received from Swedish regulatory authority.		

## Protocol synopsis (Section 1)

### *Change from:*

An iSRC charter will detail their activities, including when and which data will be reviewed, how the integrity of the study will be maintained in addition to the iSRC group membership. Once an appropriate number of subjects have completed the Week 24 assessments interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24.

### *Change to:*

An iSRC charter will detail their activities, including when and which data will be reviewed, how the integrity of the study will be maintained in addition to the iSRC group membership. **An interim analysis by the independent safety review committee will be conducted once at least 35 subjects have completed their Week 24 assessment. An additional interim analysis may be performed and this will be specified prospectively in the reporting and analysis plan.** ~~Once an appropriate number of subjects have completed the Week 24 assessments~~ Interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy ~~at Week 24.~~

## Overall Design (Section 4.1)

### *Change from:*

Once a sufficient number of subjects have completed Week 24, interim analyses and sample size re-estimation will be conducted.

### *Change to:*

An interim analysis by the independent safety review committee will be conducted once at least 35 subjects have completed their Week 24 assessment. An additional interim analysis may be performed and this will be specified prospectively in the reporting and analysis plan.

## Inclusion Criteria (Section 5.1)

### *Change from:*

- Oral Contraceptive, either combined or progestogen alone

### *Change to:*

- Combined Oral Contraceptive (note: progestogen only oral contraceptive is considered inadequate.)

*Delete:*

- ~~Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository).~~

#### **Detailed adverse event criteria (Section 5.4.2)**

*Change from:*

In addition, if any subject develops a life-threatening infection regardless of IgG status, the investigator must contact the Medical Monitor to determine whether treatment with IP should be continued.

*Change to:*

In addition, if any subject **who** develops a life-threatening infection, regardless of IgG status, **will be promptly withdrawn from IP.**~~the investigator must contact the Medical Monitor to determine whether treatment with IP should be continued.~~

#### **Permitted medications and non-drug therapies (Section 6.9.1)**

*Change from:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than 40 mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

*Change to:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than **400** mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

**Interim Analysis (Section 9.3.2)**

*Change from:*

Once an appropriate number of subjects have completed their Week 24 assessment, interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24.

*Change to:*

**An interim analysis by the independent safety review committee will be conducted once at least 35 subjects have completed their Week 24 assessment. An additional interim analysis may be performed and this will be specified prospectively in the reporting and analysis plan.** ~~Once an appropriate number of subjects have completed their Week 24 assessment, Interim analysis and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24.~~

**Regulatory and ethical considerations (Section 10.2)**

*Added:*

- Regulatory Agency review and favorable opinion/approval of the study protocol and substantial amendments.

**Appendices**

*Added:*

**Appendix 9: American-European Consensus Group Classification****References**

Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002; 61:554–8.

**Table 2** Revised international classification criteria for Sjögren's syndrome

- I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
  2. Do you have a recurrent sensation of sand or gravel in the eyes?
  3. Do you use tear substitutes more than 3 times a day?
- II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
  2. Have you had recurrently or persistently swollen salivary glands as an adult?
  3. Do you frequently drink liquids to aid in swallowing dry food?
- III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer's I test, performed without anaesthesia ( $\leq 5$  mm in 5 minutes)
  2. Rose bengal score or other ocular dye score ( $\geq 4$  according to van Bijsterveld's scoring system)
- IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue<sup>18</sup>
- V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow ( $\leq 1.5$  ml in 15 minutes)
  2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts<sup>19</sup>
  3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer<sup>20</sup>
- VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

**Table 3** Revised rules for classification*For primary SS*

In patients without any potentially associated disease, primary SS may be defined as follows:

- a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
- b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
- c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

*For secondary SS*

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

*Exclusion criteria:*

Past head and neck radiation treatment  
Hepatitis C infection  
Acquired immunodeficiency disease (AIDS)  
Pre-existing lymphoma  
Sarcoidosis  
Graft versus host disease  
Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

## 12.11. Appendix 11: Protocol changes in Amendment 2

### Amendment 2: specific amendment for Norway (all sites)

#### Protocol Amendment 02, 20th November 2015

#### Summary of Modifications (relative to original protocol) and Rationale:

1. Section 5.1 (Inclusion Criteria). This section has been updated to amend the list of acceptable methods of contraception.
2. Section 7.2 (Screening and Critical Baseline Assessments). This section has been updated to define how assessment of subjects for tuberculosis should be carried out during the screening period.
3. Section 1 (Synopsis) and Section 9.3.2 (Interim Analyses). These sections have been edited to clarify the number of subjects required for the interim analysis and the basis for the recalculation of sample size following the interim analysis.
4. Section 6.9.1 (Permitted Medications and Non-Drug Therapies). Correction of typographical error regarding the permitted dose of hydroxychloroquine.

#### Associated Protocol Modifications:

#### Protocol Cover Page

Add:

Protocol Amendment Number: 02

Add:

Author: PPD

Updated:

#### Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1
Protocol amended in response to comments received from Swedish regulatory authority.		

GlaxoSmithKline Document Number	Date	Version
2014N220285_02	2015-NOV-20	Amendment No. 2
Protocol amended in response to comments received from Norwegian regulatory authority.		

## Section 1, Synopsis, Page 11

*Delete:*

~~Once an appropriate number of subjects have completed the Week 24 assessments, interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24. Appropriate available data will be included in the interim analyses; the results of which will be reviewed by the iSRC.~~

*Add:*

The interim analysis is planned once approximately half of the subjects (i.e. 35 subjects) complete their week 24 assessment. The main purpose of the interim analysis is to assess the safety and tolerability of the study drug. In addition, on an exploratory basis, preliminary efficacy analysis will be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the dual immunotherapy.

## Inclusion Criteria (Section 5.1)

*Delete:*

- ~~• Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository).~~

## Screening and Critical Baseline Assessments (Section 7.2)

*Added:*

- **Tuberculosis:** Assessment of TB in the screening period is to be done via evaluation of the subject's history, physical examination of the subject and, if judged necessary by the Investigator, local laboratory (screening and confirmatory) testing.

## Permitted medications and non-drug therapies (Section 6.9.1)

*Change from:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than 40 mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).



*Change to:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than **400** mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

### **Interim Analysis (Section 9.3.2)**

*Delete:*

~~Once an appropriate number of subjects have completed their Week 24 assessment, interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24. Appropriate available data will be included in the interim analyses, the results of which will be reviewed by the iSRC.~~

*Add:*

The interim analysis is planned once approximately half of the subjects (i.e. 35 subjects) complete their week 24 assessment. The main purpose of the interim analysis is to assess the safety and tolerability of the study drug. Adverse events and serious adverse events, immunoglobulin levels, vital signs, blood chemistry and hematology data will be summarized by treatment.

Preliminary efficacy data will also be assessed during the interim analysis on an exploratory basis. Data such as: ESSDAI, stimulated salivary flow, oral dryness numeric response, and B cell quantification within salivary gland biopsies will be summarized by treatment and week. The purpose of this efficacy exploration is to conduct a sample size re-estimation and obtain an initial estimate of the effect size of the dual immunotherapy. As such, the variability estimates will be updated based on the emerging data with the potential of enrolling up to 120 subjects into the study to accommodate for higher than expected variability in the aforementioned efficacy endpoints. A Bayesian predictive modeling approach may be adopted to calculate predictive probabilities of success for a range of true treatment differences between the monotherapy belimumab, monotherapy rituximab and combination therapy when compared to placebo at week 24.

## 12.12. Appendix 12: Protocol changes in Amendment 3

### Amendment 3: specific amendment for Italy (all sites)

Protocol Amendment 03, 4th January 2016

#### Summary of Modifications (relative to original protocol) and Rationale:

1. Section 5.1 (Inclusion Criteria). This section has been updated to amend the list of highly effective methods of contraception.
2. Section 6.9.1 (Permitted Medications and Non-Drug Therapies). Correction of typographical error regarding the permitted dose of hydroxychloroquine.

#### Associated Protocol Modifications:

##### Protocol Cover Page

*Add:*

Protocol Amendment Number: 03

*Updated:*

#### Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1
Protocol amended in response to comments received from Swedish regulatory authority.		
2014N220285_02	2015-NOV-20	Amendment No. 2
Protocol amended in response to comments received from Norwegian regulatory authority.		
2014N220285_03	2016-JAN-04	Amendment No. 3
Protocol amended in response to comments received from Italian regulatory authority.		

**Inclusion Criteria (Section 5.1)**

*Delete:*

- ~~Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository).~~

**Permitted medications and non-drug therapies (Section 6.9.1)**

*Change from:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than 40 mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

*Change to:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than **400** mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

## **12.13. Appendix 13: Protocol changes in Amendment 4**

### **Amendment 4: global amendment (all sites).**

#### **Protocol Amendment 04, 13th June 2016**

#### **Summary of Modifications (relative to original protocol) and rationale:**

##### **1. Protocol Synopsis (Section 1)**

- The study design schematic/figure has been replaced with a revised figure which makes it easier for the reader to understand the study design. This change has also been made in Section 4 (study design).
- Clarification that a single interim analysis is planned, when that interim analysis will occur and what actions may be taken following the interim analysis.

##### **2. Study Design (Section 4)**

- Clarifications regarding the committees involved in monitoring subject safety and review of study data, the governance of the study and how these committees will work with each other during the interim analysis.
- Clarification that a single interim analysis is planned, when that interim analysis will occur and what actions may be taken following the interim analysis.
- Clearer guidance has been provided regarding the prohibition on use of topical symptomatic medications prior to efficacy assessments.
- Further information has been added in support of the use of the subcutaneous formulation of belimumab.
- The Table (Section 4.7.1) summarising the risk assessment for dual biologic therapy in primary Sjögren's syndrome has been changed, specifically the sections dealing with mitigation strategy for infections and vaccinations.
  - For the infection mitigation strategy, the protocol no longer mandates that subjects are excluded or discontinued with CD4 <400cells/mm<sup>3</sup> or CD8 <150cells/mm<sup>3</sup>. In addition, the exclusion level for IgG is now set at <550mg/dL rather than <LLN (<694mg/dL). Please refer to point 3 below for the rationale underlying these changes.
  - For the vaccination mitigation strategy, clarification is provided that live vaccination is prohibited until the end of the general or (if appropriate) the individualized follow up period. This clarification is made for practical reasons because subjects may enter the trial with B cell counts lower than the lower limit of normal, in which case they will be followed only until their B cell levels return to baseline (not until "normalization"). The individualized follow up period ends when the subject's B cell count returns to baseline (or the subject reaches week 104, whichever comes first). In addition, additional text has been added to summarise previous experience with belimumab.

- A new sub-section (Section 4.7.2) has been added to make clearer the vaccination guidance and the EULAR recommendations which underlie this guidance.

### 3. Selection of study population and withdrawal criteria (Section 5)

- The inclusion criteria have been changed.
  - Inclusion criterion #5. A change has been made which was mandated by the Italian Regulatory Authority (AIFA) and which applies only to Italian sites.
  - Inclusion criterion #6. The list of highly effective methods of contraception has been updated in to reflect most recent CTFG recommendations (2014\_09\_15) and GSK standards.
  - An additional mandatory inclusion criterion (#8) for FRANCE only, has been added.
- The exclusion criteria have been changed.
  - Exclusion criterion #20. The exception of denosumab relative to the overall exclusion of biological agents for 180days prior to Day 0 has been removed. The rationale for this is to avoid any potential increased risk of infection.
  - Exclusion criterion #30 was amended to:
    - Reduce the IgG exclusionary threshold to 550mg/dL. This level allows patients with a modest IgG hypogammaglobulinemia to enter the study. This is supported by the pivotal phase 3 study of belimumab in SLE, HGS1006-C1056 (and its long term continuation study, 112233 (C1066)) in which an IgG exclusionary threshold of <400mg/dL was used (<http://www.gsk-clinicalstudyregister.com>) and by the study of rituximab in RA (Emery, 2010; *Ann Rheum Dis*; 69:1629–1635) in which an IgG exclusionary threshold of 500 mg / dL was used. In the belimumab studies, 8 / 635 subjects developed IgG < 400 mg / dL and no subjects experiencing treatment–emergent hypogammaglobulinemia (IgG < 400 mg / dL) developed serious infection. In the rituximab study, 1.9% of rituximab treated subjects’ IgG levels declined below the lower limit of normal and no serious infections occurred in patients receiving rituximab while IgG levels were below the lower limit of normal (Emery et al., 2010; *Ann Rheum Dis*; 69:1629–1635).
    - Remove the IgM exclusion criteria. This is supported by the Rituximab Expert Consensus Committee which observed that “decreases in IgM have not been associated with increased rates of infection” and whose recommendation is to monitor IgG – but not IgM – levels during rituximab therapy (Buch et al, 2011; *Ann Rheum Dis* 2011;70:909–920).
    - Remove the CD4 and CD8 exclusion criteria and associated subject specific stopping criteria. Many patients with primary Sjogren’s

syndrome have low CD4/CD8 T-cells as part of their disease pathology. Of the first 13 potential subjects screened for this study under the original protocol, 10 potential subjects failed screening on the basis of low CD4/CD8 T-cells. Among these potential subjects CD4 T-cells ranged as low as 273 / mm<sup>3</sup> (reference range: 490-1740 / mm<sup>3</sup>) and CD8 T-cells ranged as low as 76 / mm<sup>3</sup> (reference range: 180-1170 / mm<sup>3</sup>). Furthermore, the Rituximab Expert Consensus Committee does not recommend T-cell monitoring (Buch et al, 2011; *Ann Rheum Dis* 2011;**70**:909–920). Moreover, use of CD4/CD8 T-cell selection and monitoring parameters are not part of standard clinical practice in the use of rituximab and belimumab or in the care of primary Sjögren's patients.

- Clarify that the CD19 restriction applies only to subjects previously treated with B cell depleting therapy. Potential subjects who have received B cell depleting therapy within 364 days of Day 0 are excluded from entry into this trial (Exclusion criterion # 19). Subjects whose B cells fail to reconstitute (i.e.: remain persistently below  $<0.1 \times 10^9/L$ ) a year or more after B cell depleting therapy should not participate in this study.
  - An additional mandatory exclusion criterion (#31) for FRANCE only, has been added.
- The section on screening (Section 5.3) has been amended to clarify when and how often rescreening of subjects is allowed and to clarify the criteria for repeat assessments during the screening period.
- The Section (5.4) on withdrawal/stopping criteria has been amended to:
  - Remove reference to a Week 46 “visit” which does not exist and to clarify the importance of Week 46 as a threshold for subject withdrawal with respect to pregnancy evaluation.
  - Clarify that the neurology questionnaire is a required assessment in subjects who have discontinued treatment but not withdrawn consent.
  - Added a new sub-section (Section 5.4.2) to describe the early withdrawal visit.
  - Indicate that subjects who develop a life threatening infection must be withdrawn from investigational product, regardless of IgG status.
  - Remove the stipulation that subjects will be withdrawn from investigational product based upon CD4  $<300\text{cells/mm}^3$  or CD8  $<100\text{cells/mm}^3$ .

#### 4. Study Treatment (Section 6)

- The requirements for return (by the subjects) of used and unused belimumab/placebo syringes have been clarified.
- The description of rituximab (Section 6.1.2) has been corrected and a description of the rituximab placebo (sterile saline) has been added.

- Guidance has been added for the monitoring of subjects following administration of rituximab/placebo.
- A clarification has been made regarding the meaning of “sponsor open” in the Section (6.3) describing blinding.
- The section on permitted medications (Section 6.9.1) has been amended to:
  - Correct a typographical error regarding the dose of hydroxychloroquine.
  - Provide greater detail regarding allowable topical symptomatic therapies.
- The section on prohibited medications (Section 6.9.2) has been amended to provide additional details of prohibited medications.

## **5. Study Assessments and Procedures (Section 7)**

- The Time and Events Table (Section 7.1) has been modified by the addition of “cryoglobulins” to help clarify the timing of this existing required assessment.
- Minor modifications have been made to the footnotes of the Time and Events Table to provide greater clarity and define the time window in which subjects should receive calls from the sites during the general follow up and individualized follow up phase.
- Section 7.2 and Section 7.4.5 have been altered to clarify the circumstances upon which triplicate ECG measurements should be obtained during screening. In addition, the mandatory requirement to use an ECG machine has been removed as experienced sites will be allowed to manually calculate ECG intervals.
- A new paragraph has been added to Section 7.2 to provide guidance regarding tuberculosis assessment during screening.
- Greater detail has been added to Section 7.4.1.4 regarding adverse events of special interest.
- The pregnancy Section (7.4.2) has been amended to clarify the duration of follow up.
- Some additional minor language corrections have been made throughout Section 7 to provide greater accuracy and clarity.

## **6. Statistical Considerations and Data Analysis (Section 9)**

- Clarification that a single interim analysis is planned, when that interim analysis will occur and what actions may be taken following the interim analysis. Detail has also been provided regarding the committees involved in unblinded data review at the interim analysis and what actions may be taken.
- Some changes have been made to Section 9.4.1, Section 9.4.2 & Section 9.4.3 to clarify the data analysis plans for the study. The reference to “disease related events” has been removed. This was a typographical error as there was never intention to collect data on disease related events.

**7. Study Governance Considerations (Section 10)**

- The language of Section 10.2 (Regulatory and ethical considerations) has been edited to avoid duplication and to make clear that substantial amendments are also subject to regulatory agency approval.
- Section 10.8.1 has been amended to clarify the roles of two committees which will be involved in review of unblinded data as the study progresses and to highlight that the primary governance role lies with the internal safety review committee.

**8. References (Section 11)**

- Two additional references have been added.

**9. Appendices (Section 12)**

- An additional abbreviation has been added to Appendix 1.
- Appendix 8 (Collection of Pregnancy Information) has been amended to clarify that subjects will be followed for 1 year to determine the outcome of any pregnancy.
- Appendix 9 (American European Consensus Group classification for Primary Sjögren's Syndrome) has been added.
- Appendix 10-Appendix 13 have been added. These detail changes made to the protocol in previous country specific amendments and in the current protocol amendment (version 4).

**Protocol Amendment 04: Modifications in detail:**

(New text is in bold and deleted text is marked with strikethrough).

**PROTOCOL COVER PAGE**

*Add:*

Protocol Amendment Number: 04

*Add:*

**IND (US only):** 009970

*Change author list:*

**Author (s):** <sup>PPD</sup>

[Redacted author information]



*Updated:*

### Revision Chronology

<b>GlaxoSmithKline Document Number</b>	<b>Date</b>	<b>Version</b>
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1 for Sweden
Protocol amended in response to comments received from Swedish regulatory authority.		
Local 2014N220285_02	2015-NOV-20	Amendment No. 2 for Norway
Protocol amended in response to comments received from Norwegian regulatory authority.		
Local 2014N220285_03	2016-JAN-04	Amendment No. 3 for Italy
Protocol amended in response to comments received from Italian regulatory authority.		
Global 2014N220285_04	2016-JUN-13	Amendment No. 4
<p><b>The primary reason for this amendment is to modify the subject selection criteria (specifically exclusion criterion #30 pertaining to exclusionary laboratory thresholds) to better align with the intended population characteristics.</b></p> <p><b>Other amendments include the following:</b></p> <ul style="list-style-type: none"> <li>- <b>Greater clarity is provided regarding the committees involved in monitoring subject safety and review of study data as well as the governance of the study.</b></li> <li>- <b>It has been made clear that a single formal interim analysis is planned.</b></li> <li>- <b>The subject withdrawal and study stopping criteria have been modified.</b></li> <li>- <b>Greater detail is provided regarding prohibited and permitted medications.</b></li> <li>- <b>Additional guidance is provided regarding vaccination.</b></li> <li>- <b>Guidance has been provided for tuberculosis assessment during the screening period.</b></li> <li>- <b>The pregnancy section has been modified to clarify the duration of follow up</b></li> </ul>		

required.

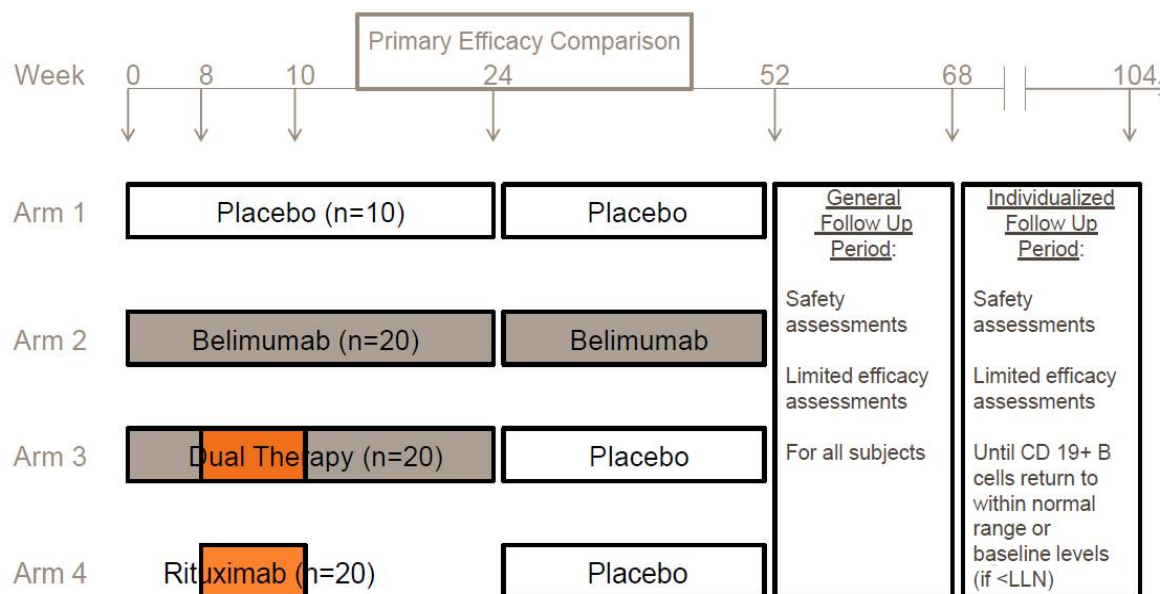
**This amendment incorporates country-specific changes required by Regulatory Authorities during prior review. In addition, changes have been made throughout to provide clarity for the conduct of the study and correct typographical errors.**

**All changes made in Amendment 4 are summarized, rationalized and detailed in Appendix 13 (Section 12.13).**

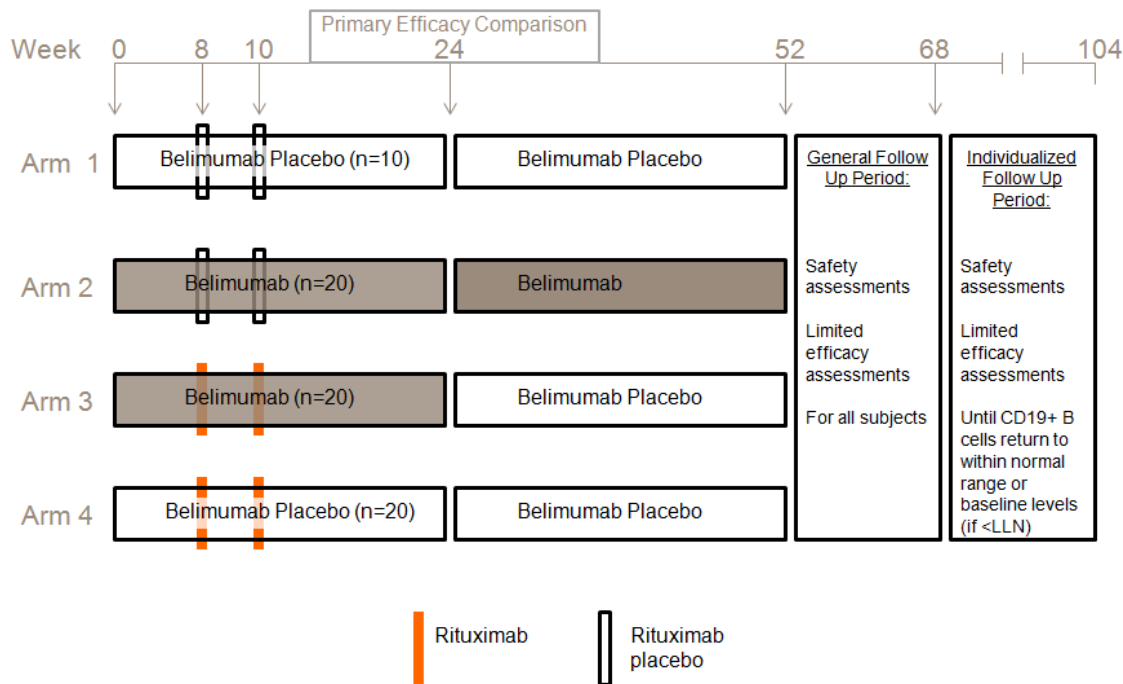
### **PROTOCOL SYNOPSIS FOR STUDY 201842 (Section 1)**

Clarification of study schematic:

*Change from:*



*Change to:*



Overall Design, Paragraph:

*Change from:*

The primary efficacy comparison for this study at Week 24 will be between the co-administration therapy arm and the placebo arm. Interim analyses will be performed on the accumulating data. Following any of the interim analyses, a number of actions could be taken: the study could continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation up to a maximum of 120 total subjects in the study.

*Overall Design, Change to:*

The primary efficacy comparison for this study at Week 24 will be between the co-administration therapy arm and the placebo arm. **Once approximately 35 subjects have completed week 24, a formal** interim analysis will be performed on the **available** accumulating data. Following ~~any of this~~ interim analysis, a number of actions could be taken: the study could continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation up to a maximum of 120 total subjects in the study.

*Interim Analysis, Change from:*

**Interim Analysis:** Study data will be reviewed in a confidential manner during the trial conduct by an internal GSK Safety Review Committee (iSRC). Reviews may include un-blinded efficacy, pharmacodynamic and safety data. An iSRC charter will detail their

activities, including when and which data will be reviewed, how the integrity of the study will be maintained in addition to the iSRC group membership. Once an appropriate number of subjects have completed the Week 24 assessments, interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24. Appropriate available data will be included in the interim analyses; the results of which will be reviewed by the iSRC. Following interim analyses, a number of actions could be taken: the study will continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.

*Change to:*

**Interim Analysis:** ~~Study data will be reviewed in a confidential manner during the trial conduct by an internal GSK Safety Review Committee (iSRC). Reviews may include unblinded efficacy, pharmacodynamic and safety data. An iSRC charter will detail their activities, including when and which data will be reviewed, how the integrity of the study will be maintained in addition to the iSRC group membership. Once an appropriate number of half of the planned subjects (i.e.: approximately 35 subjects) subjects have completed their Week 24 assessments, a formal interim analysis and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24 will take place.~~ Appropriate available **safety and efficacy** data will be included in the interim analysis. **The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy analysis will be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy.** Following the interim analysis, a number of actions could be taken: the study will continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.

## **STUDY DESIGN (Section 4)**

### **Overall design (Section 4.1)**

*Change from:*

Unblinded study data will be reviewed during trial conduct by an internal Safety Review Committee (iSRC), where a charter will detail their activities and membership. In line with routine pharmacovigilance, subjects' blinded safety data will be reviewed on an ongoing basis during the study conduct by an internal GSK Safety Review Team (SRT).

Once a sufficient number of subjects have completed Week 24, interim analyses and sample size re-estimation will be conducted. The results of the interim analyses will be reviewed by the iSRC, details of which will be outlined in the iSRC charter. Dependent on these results, the study will continue as planned, continue with modifications or may be stopped.

*Change to:*

**Study data will be reviewed in a confidential manner during the conduct of the trial.** ~~Unblinded study data will be reviewed during trial conduct by an internal Safety Review Committee (iSRC), where a charter will detail their activities and membership. In line with routine pharmacovigilance, subjects' blinded safety data will be reviewed on an ongoing basis during the study conduct by an internal GSK Safety Review Team (SRT).~~

~~Once a sufficient number of subjects have completed Week 24, interim analyses and sample size re-estimation will be conducted. The results of the interim analyses will be reviewed by the iSRC, details of which will be outlined in the iSRC charter. Dependent on these results, the study will continue as planned, continue with modifications or may be stopped.~~

**An internal GSK Safety Review Committee (iSRC), independent of the study team, will maintain governance of the study and will periodically review all available data in an un-blinded manner with a focus on key safety parameters. A Therapeutic Area (Immuno-Inflammation) Data Assessment Committee (TA DAC), independent of the study team, will periodically review un-blinded efficacy data and at the interim analysis will advise the iSRC on adaptive design changes should such changes be required. An iSRC charter details the activities of these committees, including when and which data will be reviewed, how the integrity of the study will be maintained, and the membership of both committees. Once approximately half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy analysis will be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be mandated by the iSRC: the study will continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.**

#### **Type and number of subjects (Section 4.4)**

*Add:*

**The sample size re-estimation will be conducted at the interim analysis.**

#### **Design Justification (Section 4.5)**

*Change from:*

The use of pilocarpine and cevimeline (at stable doses) as well as topical therapies (such as ophthalmic lubricants, chewing gum) may be used for symptom relief during the treatment and follow up phases but would be prohibited within 24 hours of endpoint assessments.

*Change to:*

The use of pilocarpine and cevimeline (at stable doses) as well as ~~topical~~ **symptomatic** therapies (such as ophthalmic lubricants, chewing gum) may be used for symptom relief during the treatment and follow up phases but would be prohibited ~~within 24 hours~~ **within a period of time prior to** endpoint assessments (see Section 6.9.1 for details).

#### **Dose justification (Section 4.6)**

##### **Dose Selection:**

*Added:*

**The double blind phase of this study was recently completed; the belimumab 200 mg SC weekly dose plus standard of care significantly improved SLE Response Index (SRI) and decreased time to severe flare compared with placebo plus standard of care. Furthermore, safety findings with belimumab plus standard of care were similar to that of placebo plus standard of care [Stohl, 2015].**

#### **Risk Assessment for dual biologics in pSS (Section 4.7.1)**

The table has been reformatted and the text edited to reflect revised exclusion and stopping criteria. In addition, the section on vaccination now includes further rationale with respect to belimumab.

*Change from:*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Investigational Product (IP) [belimumab (GSK1550188) &amp; rituximab]</b>		
<b><u>Infections</u></b>		
Prolonged B-cell suppression and more complete B-cell depletion expected; potential for more profound hypogammaglobulinemia with increased risk for serious infections including opportunistic infections (OIs), PML, and HBV re-activation.	<p><i>Rituximab:</i> The rate of serious infections with rituximab in the RA population is 4/100 per year.</p> <p>Reactivation of hepatitis B has also been very rarely reported in RA patients receiving rituximab.</p> <p>Late onset neutropenia occurs rarely in patients treated with rituximab.</p> <p><i>Belimumab:</i> The rate for belimumab in SLE is 5% of</p>	<p>Exclusions based on significant infection history, serologic evidence of past or present HBV or HCV infection; IgG or IgM below the LLN, IgA deficiency, neutrophils <math>&lt;1.5 \times 10^9/L</math>, <math>CD4 &lt; 400 \text{ cells/mm}^3</math>, or <math>CD8 &lt; 150 \text{ cells/mm}^3</math>.</p> <p>A PML management plan including neurologic questionnaire and patient alert card.</p> <p>Individual subject's</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>subjects receiving either belimumab or placebo.</p> <p><i>Belimumab and Rituximab:</i> Infections are expected events for both belimumab and rituximab.</p> <p>Cases of PML have been very rarely reported, including fatal events, for both rituximab and belimumab in autoimmune diseases.</p> <p><i>Dual Belimumab and Rituximab:</i> There is pre-clinical evidence for prolonged B-cell suppression and more complete B-cell depletion as well as effect on IgG1+ plasma cells in the long-lived bone marrow niche thought to be less sensitive to immunotherapy [Lin, 2015] with dual B-cell immunotherapy.</p> <p>Assessment of the translatability of the IgG reductions to humans are difficult to make due to species differences in B-cell biology and different treatments; however, the mouse data raises the hypothetical risk that immunoglobulin levels may reduce more with co-administration treatment.</p>	<p>treatment will be discontinued for (a) life-threatening infection; (b) IgG &lt;400mg/dL (or &lt;550mg/dL if associated with a serious infection); neutrophils &lt; 1X10<sup>9</sup>/L, CD4 &lt;300 cells/mm<sup>3</sup>, or CD8 &lt;100 cells/mm<sup>3</sup></p> <p>Subjects will be monitored for up to 2 years or until B-cells return to LLN and monitored for late onset neutropenia at 6 months post-rituximab.</p>
<b><u>Systemic Infusion / Injection Reactions, Hypersensitivity Reactions and Immunogenicity</u></b>		
There is a potential risk for increased ADA due to cross reactivity which could lead to increased frequency of	<i>Rituximab:</i> The incidence of serum sickness associated with rituximab in pSS studies has ranged from	ADA will be monitored with collection at baseline, Weeks 8, 24, and 52

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<p>hypersensitivity reactions, particularly of the delayed type.</p> <p><u>Serum Sickness:</u> The incidence of serum sickness associated with rituximab is higher in autoimmune indications and likely greater in Sjögren's Syndrome vs. RA [Meijer, 2010].</p>	<p>6-38% [Carubbi, 2014].</p> <p><i>Belimumab and Rituximab:</i> Administration of belimumab and rituximab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Delay in the onset of serious hypersensitivity reactions can occur. Both rituximab and belimumab have been associated with delayed type non-acute HSR/serum sickness, although no relationship to ADA has been established.</p> <p><i>Dual Belimumab and Rituximab:</i> Incidences of hypersensitivity and infusion reactions have been noted to be higher with co-administration vs. mono-biologic therapy but no association with ADA has been established [Weinblatt, 2006].</p>	<p>A pre-medication regimen will be given before each rituximab/rituximab placebo infusion: methylprednisolone 100 mg IV, an oral antihistamine and analgesic.</p> <p>Patients will be given an alert card for HSR and delayed HSR/serum sickness.</p>
<b><u>Malignancy</u></b>		
<p>There is an increased risk of B-cell lymphoma in pSS. There is a theoretical increased risk of malignancy with combination immunosuppressive mechanisms; however, the potential synergistic effect of rituximab/belimumab would be assumed to result in a prolonged b-cell depletion that would not be dissimilar to repeat doses of rituximab.</p>	<p><i>Belimumab and Rituximab:</i> Immunomodulatory drugs like rituximab and belimumab may increase the risk of malignancy. To date, no causal relationship to belimumab or rituximab to malignancy, including B-cell lymphoma, has been detected with either agent, both of which have been administered long term and in combination with other immunosuppressants of various mechanisms.</p>	<p>Subjects with a history of malignancy in the 5 yrs prior to randomization will be excluded (see Section 5.2, criterion #4).</p>



Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b><u>Interaction with Vaccinations</u></b>		
There is a risk of reduced antibody titers with mono and dual B cell immunotherapy. The potential synergistic effect of rituximab and belimumab may result in a prolonged B-cell depletion that should have a similar impact on vaccine response as administering repeated doses of rituximab.	<i>Rituximab:</i> Median antibody titers (tetanus, diphtheria, pneumococcus) at Week 32 were reduced from baseline in atacicept but not placebo-treated patients who had been previously treated with rituximab. However, these values recovered close to baseline by Week 16 of the follow-up, there were few shifts to below protective titres, and no between-group differences with respect to the frequency of shifts.	Live vaccination is prohibited from 30 days prior to Day 1 until normalization of peripheral B cells.  Subjects' vaccination status should be assessed and current immunization guidelines followed; all necessary vaccinations should be administered if possible no later than 30 days prior to Day 0.
<b><u>Psychiatric Events</u></b>		
There is a potential risk of psychiatric events with belimumab and rituximab.	<i>Rituximab:</i> Depression and anxiety were common adverse events in rituximab RA trials.  <i>Belimumab:</i> There have been reports of depression and suicidality in patients receiving belimumab. A causal relationship to belimumab has not been established.	Subjects who, in the investigator's opinion, pose a significant suicide risk will be excluded.  The C-SSRS will be completed at each visit during which the subject may potentially be exposed to belimumab.  Subjects will be monitored closely for signs and symptoms of psychiatric illness including depression and suicidal ideation. Subjects displaying such signs and symptoms will be treated appropriately and referred as necessary to specialty psychiatric care.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b><u>Cardiac disorders</u></b>		
	<p><i>Rituximab:</i> Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. There is no data on the safety of rituximab in patients with moderate to severe heart failure or severe, uncontrolled CV disease.</p> <p><i>Belimumab and Rituximab:</i> Hypotension may accompany infusion/post-injection systemic reactions with both rituximab and belimumab.</p>	<p>Exclude subjects with severe heart failure (New York Heart Association, Class IV) or other severe, uncontrolled cardiac disease.</p> <p>Closely monitor any patients with cardiac history or those who have experienced prior cardiopulmonary adverse reactions during administration of rituximab/rituximab placebo. Consider withholding anti-hypertensive medications 12 hours prior to rituximab/rituximab placebo infusion.</p>
<b><u>Skin reactions</u></b>		
	<p><i>Rituximab:</i> Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome; some with fatal outcome, have been reported with rituximab.</p>	<p>Permanently discontinue treatment in the case of such an event with suspected relationship to treatment.</p>
<b><u>Posterior Reversible Encephalopathy Syndrome (PRES)</u></b>		
	<p><i>Rituximab:</i> Cases of PRES / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without</p>	<p>Medical monitor will be notified of any new neurologic symptoms (see Section 5.4.3). Medical monitor and investigator will consider the possibility of PRES in differential diagnosis.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.	
<b>Study Procedures</b>		
<b><u>Salivary gland Biopsy</u></b>		
This procedure is associated with (a low) incidence of complications including bleeding and hematoma formation.	The reported incidence of bleeding and hematoma were 7.5% and 2.7%, respectively in a large case series [Santiago, 2012].	Subjects will be instructed to stop anticoagulant therapy (i.e., aspirin, NSAIDs, warfarin) prior to the procedure. Also, the biopsy will be performed by qualified physicians, surgeons or dentists and the personnel performing the biopsy will be required to undergo study-specific training in the performance of this procedure.

*Change to:*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Investigational Product (IP) [belimumab (GSK1550188) &amp; rituximab]</b>		
<b><u>Infections</u></b>		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<p><b><u>Infections:</u></b></p> <p>Prolonged B-cell suppression and more complete B-cell depletion expected; potential for more profound hypogammaglobulinemia with increased risk for serious infections including opportunistic infections (OIs), PML, and HBV re-activation.</p>	<p><i>Rituximab:</i> The rate of serious infections with rituximab in the RA population is 4/100 per year.</p> <p>Reactivation of hepatitis B has also been very rarely reported in RA patients receiving rituximab.</p> <p>Late onset neutropenia occurs rarely in patients treated with rituximab.</p> <p><i>Belimumab:</i> The rate for belimumab in SLE is 5% of subjects receiving either belimumab or placebo.</p> <p><i>Belimumab and Rituximab:</i> Infections are expected events for both belimumab and rituximab.</p> <p>Cases of PML have been very rarely reported, including fatal events, for both rituximab and belimumab in autoimmune diseases.</p> <p><i>Dual Belimumab and Rituximab:</i> There is pre-clinical evidence for prolonged B-cell suppression and more complete B-cell depletion as well as effect on IgG1+ plasma cells in the long-lived bone marrow niche thought to be less sensitive to immunotherapy [Lin, 2015] with dual B-cell immunotherapy. Assessment of the translatability of the IgG reductions to humans is</p>	<p>Exclusions based on significant infection history, serologic evidence of past or present HBV or HCV infection; IgG &lt; 550 mg / dL or IgM below the LLN, IgA deficiency, neutrophils &lt; 1.5X10<sup>9</sup>/L, <del>CD4 &lt; 400 cells/mm<sup>3</sup>, or CD8 &lt; 150 cells/mm<sup>3</sup>.</del></p> <p>A PML management plan including neurologic questionnaire and patient alert card.</p> <p>Individual subject's treatment will be discontinued for (a) life-threatening infection; (b) IgG &lt; 400mg/dL (or &lt; 550mg/dL if associated with a serious infection); (c) neutrophils &lt; 1X10<sup>9</sup>/L, <del>CD4 &lt; 300 cells/mm<sup>3</sup>, or CD8 &lt; 100 cells/mm<sup>3</sup></del></p> <p>Subjects will be monitored for up to 2 years or until B-cells return to LLN and monitored for late onset neutropenia at 6 months post-rituximab.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	difficult to make due to species differences in B-cell biology and different treatments; however, the mouse data raises the hypothetical risk that immunoglobulin levels may reduce more with co-administration treatment.	
<b><u>Systemic Infusion / Injection Reactions, Hypersensitivity Reactions and Immunogenicity</u></b>		
<p><b><u>Systemic Infusion / Injection Reactions, Hypersensitivity Reactions and Immunogenicity</u></b></p> <p>There is a potential risk for increased ADA due to cross reactivity which could lead to increased frequency of hypersensitivity reactions, particularly of the delayed type.</p> <p><u>Serum Sickness:</u> The incidence of serum sickness associated with rituximab is higher in autoimmune indications and likely greater in Sjögren's Syndrome vs. RA [Meijer, 2010].</p>	<p><i>Rituximab:</i> The incidence of serum sickness associated with rituximab in pSS studies has ranged from 6-38% [Carubbi, 2014].</p> <p><i>Belimumab and Rituximab:</i> Administration of belimumab and rituximab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Delay in the onset of serious hypersensitivity reactions can occur. Both rituximab and belimumab have been associated with delayed type non-acute HSR/serum sickness, although no relationship to ADA has been established.</p> <p><i>Dual Belimumab and Rituximab:</i> Incidences of hypersensitivity and infusion reactions have been noted to be higher with co-administration vs. mono-biologic therapy but no association with ADA has been established</p>	<p>ADA will be monitored with collection at baseline, Weeks 8, 24, and 52</p> <p>A pre-medication regimen will be given before each rituximab/rituximab placebo infusion: methylprednisolone 100 mg IV, an oral antihistamine and analgesic.</p> <p>Patients will be given an alert card for HSR and delayed HSR/serum sickness.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	[Weinblatt, 2006].	
<b><u>Malignancy</u></b>		
<b><u>Malignancy</u></b>  There is an increased risk of B-cell lymphoma in pSS. There is a theoretical increased risk of malignancy with combination immunosuppressive mechanisms; however, the potential synergistic effect of rituximab/belimumab would be assumed to result in a prolonged b-cell depletion that would not be dissimilar to repeat doses of rituximab.	<i>Belimumab and Rituximab:</i> Immunomodulatory drugs like rituximab and belimumab may increase the risk of malignancy. To date, no causal relationship to belimumab or rituximab to malignancy, including B-cell lymphoma, has been detected with either agent, both of which have been administered long term and in combination with other immunosuppressants of various mechanisms.	Subjects with a history of malignancy in the 5 yrs prior to randomization will be excluded (see Section 5.2, criterion #4).
<b><u>Interaction with Vaccinations</u></b>		
<b><u>Interaction with Vaccinations</u></b>  There is a risk of reduced antibody titers with mono and dual B cell immunotherapy. The potential synergistic effect of rituximab and belimumab may result in a prolonged B-cell depletion that should have a similar impact on vaccine response as administering repeated doses of rituximab.	<i>Rituximab:</i> Median antibody titers (tetanus, diphtheria, pneumococcus) at Week 32 were reduced from baseline in atacicept but not placebo-treated patients who had been previously treated with rituximab. However, these values recovered close to baseline by Week 16 of the follow-up, there were few shifts to below protective titres, and no between-group differences with respect to the frequency of shifts.  <i>Belimumab:</i> the efficacy of concurrent vaccination in patients receiving belimumab is not known; however, in the	Live vaccination is prohibited from 30 days prior to Day 0 until <del>normalization of peripheral B-cells.</del> <b>the end of the general follow up period or IFU, if appropriate.</b>  Subjects' vaccination status should be assessed and current immunization guidelines followed; all necessary vaccinations should be administered if possible no later than 30 days prior to Day 0.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	belimumab vaccination trial (study 115470, see GSK Clinical Study Register at <a href="http://www.gsk-clinicalstudyregister.com">www.gsk-clinicalstudyregister.com</a> ), evaluation of the impact of belimumab treatment on response to on-treatment vaccination with 23-valent pneumococcal vaccine revealed that immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.	
<b><u>Psychiatric Events</u></b>		
<b><u>Psychiatric Events</u></b>  There is a potential risk of psychiatric events with belimumab and rituximab.	<i>Rituximab:</i> Depression and anxiety were common adverse events in rituximab RA trials.  <i>Belimumab:</i> There have been reports of depression and suicidality in patients receiving belimumab. A causal relationship to belimumab has not been established.	Subjects who, in the investigator's opinion, pose a significant suicide risk will be excluded.  The C-SSRS will be completed at each visit during which the subject may potentially be exposed to belimumab.  Subjects will be monitored closely for signs and symptoms of psychiatric illness including depression and suicidal ideation. Subjects displaying such signs and symptoms will be treated appropriately and referred as necessary to specialty psychiatric care.
<b><u>Cardiac disorders</u></b>		
<b><u>Cardiac disorders</u></b>	<i>Rituximab:</i> Angina pectoris, cardiac arrhythmias such as	Exclude subjects with severe heart failure (New

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. There is no data on the safety of rituximab in patients with moderate to severe heart failure or severe, uncontrolled CV disease.</p> <p><i>Belimumab and Rituximab:</i> Hypotension may accompany infusion/post-injection systemic reactions with both rituximab and belimumab.</p>	<p>York Heart Association, Class IV) or other severe, uncontrolled cardiac disease.</p> <p>Closely monitor any patients with cardiac history or those who have experienced prior cardiopulmonary adverse reactions during administration of rituximab/rituximab placebo. Consider withholding anti-hypertensive medications 12 hours prior to rituximab/rituximab placebo infusion.</p>
<b><u>Skin reactions</u></b>		
<b><u>Skin reactions</u></b>	<i>Rituximab:</i> Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome; some with fatal outcome, have been reported with rituximab.	Permanently discontinue treatment in the case of such an event with suspected relationship to treatment.
<b><u>Posterior Reversible Encephalopathy Syndrome (PRES)</u></b>		
<b><u>Posterior Reversible Encephalopathy Syndrome (PRES)</u></b>	<i>Rituximab:</i> Cases of PRES / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported	Medical monitor will be notified of any new neurologic symptoms (see Section 5.4.3). Medical monitor and investigator will consider the possibility of PRES in differential diagnosis.



Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.	
<b>Study Procedures</b>		
<b><u>Salivary gland Biopsy</u></b>		
<b><u>Salivary gland Biopsy</u></b> This procedure is associated with (a low) incidence of complications including bleeding and hematoma formation.	The reported incidence of bleeding and hematoma were 7.5% and 2.7%, respectively in a large case series [Santiago, 2012].	Subjects will be instructed to stop anticoagulant therapy (i.e., aspirin, NSAIDs, warfarin) prior to the procedure. Also, the biopsy will be performed by qualified physicians, surgeons or dentists and the personnel performing the biopsy will be required to undergo study-specific training in the performance of this procedure.

### **Vaccinations (Section 4.7.2)**

A new Section 4.7.2 has been added to emphasise the vaccination recommendations and reference the appropriate EULAR guidelines.

*Add:*

The vaccination risk mitigation strategy detailed in the table above recommends that all necessary vaccinations should be administered if possible no later than 30 days prior to day 0 and requires that no live vaccine be given from 30 days prior to day 0 until the end of the general follow up period or IFU, if appropriate. In determining which vaccinations are necessary, investigators should follow guidelines such as the EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (van Assen et al., 2011). If indicated for standard of care, non live vaccines (e.g., inactivated influenza vaccines) may be administered while on study based on an assessment of the benefit:risk (e.g.: theoretical risk of decreased responsiveness).

**SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA**  
**(Section 5)**

**Inclusion Criteria (Section 5.1)**

**Criterion #5**

*Change from:*

Systemically active disease, ESSDAI  $\geq 5$  points.

*Change to:*

Systemically active disease, ESSDAI  $\geq 5$  points.

**OR (for sites in ITALY ONLY)**

**Systemically active disease, ESSDAI  $\geq 5$  points and with at least:**

- c) 1 extraglandular domain moderate,**
- OR**
- d) 2 extraglandular domains low.**

**Criterion #6:**

*Change from:*

Oral Contraceptive, either combined or progestogen alone

*Change to:*

**Combined estrogen and progestogen oral contraceptive**

*Delete:*

~~Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository).~~

**New inclusion criterion #8**

*Add:*

**For FRANCE ONLY, a subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category. It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.**

**Exclusion Criteria (Section 5.2)****Exclusion criterion #14**

*Add:*

**(refer to Section 7.4.5)**

**Exclusion criterion #20**

*Change from:*

Have received abatacept or any biologic agent within 180 day prior to Day 0 (with exception of denosumab)

*Change to:*

Have received abatacept or any biologic agent within 180 day prior to Day 0 (~~with exception of denosumab~~)

**Exclusion criterion #30**

*Change from:*

Any of the following screening laboratory values:

- White blood cells (WBC)  $<2 \times 10^9/\text{L}$
- Neutrophils  $<1.5 \times 10^9/\text{L}$
- Circulating IgG or IgM levels  $<$ lower limit of normal (according to central laboratory range)
- Aspartate aminotransferase (AST)  $>2.0$  times the upper limit of normal
- Alkaline phosphatase (ALP)  $>1.5$  times the upper limit of normal
- Bilirubin  $>1.5$  times the upper limit of normal
- CD4 count  $<400 \text{ cells}/\text{mm}^3$
- CD8 count  $<150 \text{ cells}/\text{mm}^3$

CD19+ B-lymphocyte counts  $<0.1 \times 10^9/\text{L}$

*Change to:*

Any of the following screening laboratory values:

- White blood cells (WBC)  $<2 \times 10^9/\text{L}$
- Neutrophils  $<1.5 \times 10^9/\text{L}$
- Circulating IgG  $< 550 \text{ mg} / \text{dL}$  or IgM levels  $<$ lower limit of normal (~~according to central laboratory range~~)

- Aspartate aminotransferase (AST) >2.0 times the upper limit of normal
- Alkaline phosphatase (ALP) >1.5 times the upper limit of normal
- Bilirubin >1.5 times the upper limit of normal (**unless direct bilirubin fraction is < 35%**)
- ~~CD4 count <400 cells/mm<sup>3</sup>~~
- ~~CD8 count <150 cells/mm<sup>3</sup>~~
- CD19+ B-lymphocyte counts <0.1 x 10<sup>9</sup>/L (**applies only to subjects previously exposed to B cell depleting therapies**)

### **New Exclusion criterion #31**

*Add:*

**For FRANCE ONLY, subjects with legal or administrative guardianship (“tutelle” or “curatelle”), or subjects deprived of liberty, or subjects receiving psychiatric care, or subjects hospitalized in an Health and Social Establishment for purposes other than participation in this study.**

### **Screening/Baseline/Run-in failures (Section 5.3)**

*Change from:*

Subjects who fail screening as a result of negative auto-antibodies (SS-A and SS-B) or as a result of insufficient systemic disease activity (ESSDAI ≤5 points) may be rescreened once in the 12 month period following the initial screen if the investigator has reason to believe that the subject’s auto-antibody status or level of systemic disease activity has changed. Similarly, subjects who are excluded on the basis of abnormal laboratory screening values as detailed in Selection Criteria #30 (Section 5.2) may be re-screened within a 1 year period if the investigator has reason to believe the laboratory values may have changed. The informed consent process should be repeated in the event that a subject is rescreened.

Assessments may be repeated in cases of technical malfunction (e.g., loss of laboratory specimen). Assessments (see Section 7.1) performed during the 35 day screening period to determine subject suitability for entry into the study may be repeated during this screening period. These are repeat assessments and not rescreening events.

*Change to:*

**Rescreening:** ~~Subjects who fail screening as a result of negative auto-antibodies (SS-A and SS-B) or as a result of insufficient systemic disease activity (ESSDAI ≤5 points) may be rescreened once in the 12 month period following the initial screen if the investigator has reason to believe that the subject’s auto-antibody status or level of systemic disease activity has changed. Similarly, subjects who are excluded on the basis of abnormal laboratory screening values as detailed in Selection Criteria #30 (Section 5.2) may be re-~~

~~screened within a 1 year period if the investigator has reason to believe the laboratory values may have changed. The informed consent process should be repeated in the event that a subject is rescreened.~~ **Subjects who fail screening may be rescreened once at the discretion of the investigator.**

~~Assessments may be repeated in cases of technical malfunction (e.g., loss of laboratory specimen). Assessments (see Section 7.1) performed during the 35 day screening period to determine subject suitability for entry into the study may be repeated during this screening period. These are repeat assessments and not rescreening events.~~

**Repeat assessments during the 35 day screening period: assessments (see Section 7.1), including laboratory assessments, may be repeated if determined necessary by the investigator, for example: (a) in cases of technical malfunction (e.g., loss of laboratory specimen), (b) in the event of a value close enough to the exclusionary threshold that it may reasonably lie within the degree of variability of the assay; (c) if there is reason to believe the result may be false (i.e.: contradicts recent result for the same parameter). These are repeat assessments and not rescreening events. If the original result was exclusionary and is confirmed by repeat testing, the subject will be excluded.**

#### **Withdrawal/Stopping Criteria/General Criteria (Section 5.4.1)**

*Change from:*

In addition, for a subset of subjects who receive rituximab/placebo at the Week 8 visit, or at both the Weeks 8 and 10 visits, but who discontinue treatment prior to the Week 46 visit, maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until approximately 52 weeks after the last dose of rituximab/pbo was administered.

Subject discontinues treatment before the Week 8 Visit	Subject discontinues treatment after the Week 8 Visit and before the Week 46 Visit	Subject discontinues treatment at or after the Week 46 Visit
<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, AEs, SAEs, and concomitant medications during the 16-week general follow-up period</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ An additional telephone call for urine pregnancy results at approximately 52 weeks after the last rituximab/placebo dose</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>

*Change to:*

In addition, for a subset of subjects who receive rituximab/placebo at the Week 8 visit, or at both the Weeks 8 and 10 visits, but who discontinue treatment prior to the Week 46 visit, maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until approximately 52 weeks after the last dose of rituximab/pbo was administered.

**Week 46 is an important threshold for withdrawal as it is only beyond week 46 that continued exposure to belimumab/placebo dictates a longer follow up for pregnancy evaluation (Section 7.4.2).**

Subject discontinues treatment before the Week 8 Visit	Subject discontinues treatment after the Week 8 Visit and before the Week 46 Visit	Subject discontinues treatment at or after the Week 46 Visit
<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, <b>neurological questionnaire</b>, AEs, SAEs, and concomitant medications during the 16-week general follow-up period</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, <b>neurological questionnaire</b>, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ An additional telephone call for urine pregnancy results at approximately 52 weeks after the last rituximab/placebo dose</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, <b>neurological questionnaire</b>, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>

**Please refer to Section 5.4.4 of the study reference manual for further consideration of scenarios which may be encountered in terms of the timing and circumstances of subject withdrawal and the steps which need to be followed.**

#### **Early withdrawal visit (Section 5.4.2)**

A new section has been created to describe the early withdrawal visit.

*Add:*

**Subjects that withdraw consent prior to the week 68 visit should, if possible, complete an early withdrawal visit. The early withdrawal visit is identical to the week 68 visit (see Section 7.1) but also includes the exit interview (Section 7.3.1).**

#### **Detailed adverse event criteria (Section 5.4.3)**

*Change from:*

All subjects should be monitored closely for infection. Patients who develop IgG <400 mg/dL confirmed by repeat test 1 week (>2 days) after the initial result, will be withdrawn from study treatment. In addition, increased vigilance for infection is recommended in subjects who develop IgG <550 mg/dL. Those with a decrease in IgG

below 550 mg/dL that is associated with a serious infection (i.e., an infection reported as an SAE) will be withdrawn from study treatment. In addition, if any subject develops a life-threatening infection regardless of IgG status, the investigator must contact the Medical Monitor to determine whether treatment with IP should be continued. Finally, subjects will be withdrawn from study treatment for the following lab abnormalities: neutrophils  $<1 \times 10^9/L$ , CD4  $<300 \text{ cells/mm}^3$ , or CD8  $<100 \text{ cells/mm}^3$  (confirmed by repeat test 1 week [ $>2$  days] after the initial result).

*Change to:*

All subjects should be monitored closely for infection. Patients who develop IgG  $<400 \text{ mg/dL}$  confirmed by repeat test 1 week ( $>2$  days) after the initial result, will be withdrawn from study treatment. In addition, increased vigilance for infection is recommended in subjects who develop IgG  $<550 \text{ mg/dL}$ . Those with a decrease in IgG below 550 mg/dL that is associated with a serious infection (i.e., an infection reported as an SAE) will be withdrawn from study treatment. In addition, ~~if any subject who~~ **will be promptly withdrawn from the investigator must contact the Medical Monitor to determine whether treatment with IP should be continued.** Finally, subjects will be withdrawn from study treatment for the following lab abnormalities **abnormality**: neutrophils  $<1 \times 10^9/L$ , CD4  $<300 \text{ cells/mm}^3$ , or CD8  $<100 \text{ cells/mm}^3$  (confirmed by repeat test 1 week [ $>2$  days] after the initial result).

## **STUDY TREATMENT (Section 6)**

### **Self Administered Subcutaneous Injections and Log Book (Section 6.1.1.1)**

Paragraph 2:

*Change from:*

Subjects will remain at the clinic for 3 hours following the first and the second dose of belimumab for observation.

*Change to:*

Subjects will remain at the clinic for 3 hours following the first and the second dose of belimumab/**placebo** for observation.

Paragraph 4:

*Change from:*

Subjects will be provided with a self-injection log book. Subjects will fill out the injection log immediately after administering the injection, recording the date of injection, the injection site and whether or not the entire dose was administered. If the entire dose was not administered, an explanation should be provided, and the estimated amount injected should be recorded. The injection site should be rotated between the left or the right thigh and the abdomen. Dosing compliance should be reviewed with the



subject monthly at the site study visit and self-injection log books collected from the subject by study site staff. Subjects are also required to return all used syringes at each visit, and all unused syringes at their final visit

*Change to:*

Subjects will be provided with a self-injection log book (**refer to Appendices of Study Reference Manual**). Subjects will fill out the injection log immediately after administering the injection, recording the date of injection, the injection site and whether or not the entire dose was administered. If the entire dose was not administered, an explanation should be provided, and the estimated amount injected should be recorded. The injection site should be rotated between the left or the right thigh and the abdomen. Dosing compliance should be reviewed with the subject monthly at the site study visit and self-injection log books ~~collected from the subject~~ **reviewed** by study site staff. Subjects are also required to return all ~~unused~~ **used** syringes at each **study** visit. ~~and all unused syringes should be placed in a sharps container and returned to the site as described in Section 2 of the Study Reference Manual at their final visit.~~

### **Rituximab (Section 6.1.2)**

Paragraph 2:

*Change from:*

Rituximab is a 100 mg concentrated solution for infusion. It is a clear, colorless liquid. Rituximab and placebo will be prepared at the study site by an unblinded pharmacist according to the procedure defined in the Pharmacy Manual. Rituximab treatment will consist of two 1000 mg intravenous infusions, a first 1000 mg intravenous infusion followed by a second 1000 mg intravenous infusion 2 weeks later.

*Change to:*

Rituximab is a ~~5~~100 mg concentrated solution **which requires dilution prior to** ~~for~~ infusion. It is a clear, colorless liquid. Rituximab and placebo **(0.9% NaCl, sterile, pyrogen free)** will be prepared at the study site by an unblinded pharmacist according to the procedure defined in the Pharmacy Manual. Rituximab treatment will consist of two 1000 mg intravenous infusions, a first 1000 mg intravenous infusion followed by a second 1000 mg intravenous infusion 2 weeks later. **Please refer to the study reference manual for guidance regarding missed doses of rituximab.**

Paragraph 4:

*Change from:*

The rituximab/placebo solution prepared by the unblinded pharmacist should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion

interrupted immediately. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of clinical investigations including laboratory values. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

*Change to:*

The rituximab/placebo solution prepared by the unblinded pharmacist should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. **As detailed in the rituximab summary of product characteristics, patients should be closely monitored for the onset of infusion reactions during the rituximab/placebo infusion. Vital signs (heart rate, blood pressure, temperature and respiratory rate) should be regularly measured and subjects should be observed closely for any signs that might be consistent with a hypersensitivity reaction (e.g. development of skin rash, fever). Patients should be closely monitored for the onset of cytokine release syndrome.** Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion interrupted immediately. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of clinical investigations including laboratory values. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

**Blinding (Section 6.3)**

Final bullet point:

*Change from:*

- Sponsor open refers only to those members of the iSRC who are unblinded for the interim analysis, as outlined in the iSRC charter. The GSK study team will be blinded except for any iSRC team members and any team members required for monitoring the pharmacy e.g., unblinded monitor etc.

*Change to:*

- Sponsor open refers only to those members of the iSRC **and the TA DAC** who are unblinded for the interim analysis, as outlined in the iSRC charter. The GSK study team will be blinded except for any ~~iSRC team members and any~~ team members required for monitoring the pharmacy e.g., unblinded monitor etc.

**Permitted medications and non-drug therapies (Section 6.9.1)**

Bullet point 2:

*Change from:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than 40 mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

*Change to:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than **400** mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

Bullet point 3:

*Change from:*

- Topical symptomatic therapies (such as ophthalmic lubricants). Subjects will be required to withhold dosing with these agents in the 24h prior to all efficacy assessments.

*Change to:*

- Topical symptomatic therapies **are detailed below:**
  - ~~(such as~~ Ophthalmic lubricants (e.g. glucane or saline eye drops); **subjects will be required to withhold dosing 4hrs prior to efficacy assessments.**
  - **Ophthalmic lubricating ointments [(e.g. Dry Eyes, LacriLube); subjects will be required to withhold dosing 24hrs prior to efficacy assessments].**
  - Hydroxyl cellulose ophthalmic insert [(e.g. Lacrisert); subjects will be required to withhold dosing **24hrs prior to efficacy assessments].**
  - **Non-pharmacologic saliva stimulants [(e.g. gums, drinks, teeth washing); subjects will be required to withhold dosing 90 minutes prior to efficacy assessments].**
  - **Saliva substitutes [(e.g. Xialine, Oral Balance , Saliva Orthana , Salinum mouth rinses, Chlorhexidine mouth rinses); subjects will be required to withhold dosing 90 minutes prior to efficacy assessments.**

~~Subjects will be required to withhold dosing with these agents in the 24 h prior to all efficacy assessments.~~

**Prohibited Medications and Non-Drug Therapies (Section 6.9.2)**

*Change from:*

- Concomitant biologic treatments

- Conventional systemic immunosuppressive treatments and DMARDs (such as methotrexate and azathioprine)

*Change to:*

- Concomitant biologic treatments (**see SRM for examples**)
- Conventional systemic immunosuppressive treatments and DMARDs (such as methotrexate and azathioprine)
- **Pharmacological topical ophthalmic agents (e.g. NSAIDs, corticosteroids, cyclosporine, diquafosal) are excluded from use in the study.**
- **Non muscarinic secretagogues (e.g. Anetholtritione, Bromhexine3 N-acetylcystein) are excluded from use in the study.**

## **STUDY ASSESSMENTS AND PROCEDURES (Section 7)**

### **Time and Events Table (Section 7.1)**

Safety and Laboratory Assessments:

*Added:*

**Blood: Cryoglobulins.** An additional row has been added to the table to clarify when blood samples should be taken for cryoglobulins assessment.

Footnote 1:

*Change from:*

All subjects, including subjects who are withdrawn from the study (See Section 5.4.1) and decline to complete the treatment phase visits through Week 52, are required to enter the general follow up period. During this 16-week general follow up period, subjects will receive monthly calls to evaluate AEs, to check concomitant medications and to complete the neurological assessment (Appendix 5).

*Change to:*

All subjects, including subjects who are withdrawn from the study (See Section 5.4.1) and decline to complete the treatment phase visits through Week 52, are required to enter the general follow up period. During this 16-week general follow up period, subjects will receive ~~monthly~~ calls **every 4 weeks ( $\pm 7$  days)** to evaluate AEs, to check concomitant medications and to complete the neurological assessment (Appendix 5).

Footnote 2:

*Change from:*

In order to maintain the blind, sites will be blinded to these data - including B-cell flow cytometry panels and IgA, IgM levels.

*Change to:*

In order to maintain the blind, sites will be blinded to these data **following screening** - including B-cell flow cytometry panels and IgA, IgM levels.

Footnote 6, first sentence:

*Change from:*

Subjects will enter the IFU if, following the general follow up period, their CD19+ B-cell levels remain below the lower limit of normal (or less than 90% of baseline, if baseline value was below LLN). During the IFU, subjects will be seen in the clinic every 12 weeks ( $\pm 7$  days), with monthly calls between visits to evaluate subjects for AEs & concomitant medications.

*Change to:*

Subjects will enter the IFU if, following the general follow up period, their CD19+ B-cell levels remain below the lower limit of normal (or less than 90% of baseline, if baseline value was below LLN). During the IFU, subjects will be seen in the clinic every 12 weeks ( $\pm 7$  days), with ~~monthly~~ calls **every 4 weeks ( $\pm 7$  days)** between visits to evaluate subjects for AEs & concomitant medications.

Footnote 8:

*Change from:*

Both doses of rituximab/placebo will be administered in the clinic. 60 minutes prior to rituximab subjects will receive orally an antipyretic and an antihistamine. 30-60 minutes prior to administration of rituximab/placebo, subjects will receive IV 100mg methylprednisilone .The 2nd rituximab/placebo administration at the Week10 visit must be given 14 days after the first administration (given at the Week 8 visit). A patient alert card should be sent home with the subject following each dose of rituximab.

*Change to:*

Both doses of rituximab/placebo will be administered in the clinic. 60 minutes prior to rituximab/**placebo**, subjects will receive orally an antipyretic and an antihistamine. 30-60 minutes prior to administration of rituximab/placebo, subjects will receive IV 100mg methylprednisilone .The 2nd rituximab/placebo administration at the Week10 visit must be given 14 days after the first administration (given at the Week 8 visit). A patient alert card should be sent home with the subject following each dose of rituximab/**placebo**.

Footnote 10:

*Change from:*

Subjects will receive a reminder phone call 48 hours prior to efficacy assessment visits to remind them that they should not be using topical symptomatic therapy for 24 hours prior to visit; in addition subjects should document their last use of topical symptomatic therapy.

*Change to:*

Subjects will receive a reminder phone call 48 hours prior to efficacy assessment visits to remind them that they should not be using ~~topical~~ **certain** symptomatic therapies ~~for 24 hours prior to visit~~ **(see Section 4.1 of Study Reference Manual for details)**; in addition subjects should document their last use of ~~topical~~ symptomatic therapies **in their self injection log book.**

### **Screening and Critical Baseline Assessments (Section 7.2)**

#### **Electrocardiogram**

*Change from:*

**Electrocardiogram:** Triplicate 12-lead ECGs will be obtained at screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. A single method (Bazett's or Fredericia's) must be used when calculating the corrected QT interval for determining subject eligibility, as described in the SRM.

*Change to:*

**Electrocardiogram:** ~~Triplicate~~ 12-lead ECGs will be obtained at screening ~~using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.~~ A single method (Bazett's or Fredericia's) must be used when calculating the corrected QT interval for determining subject eligibility, as described in the **study reference manual (SRM).**

#### **Tuberculosis (new subsection):**

*Added:*

- **Tuberculosis:** Assessment of TB in the screening period is to be done via evaluation of the subject's history, physical examination of the subject and, if judged necessary by the Investigator, local laboratory (screening and confirmatory) testing.

**Salivary gland biopsy:***Change from:*

The salivary gland biopsy surgical technique will be described in the SRM and training. Training reference materials will be provided to site personnel who will perform this procedure.

Biopsy tissue will be shipped to a central histopathology laboratory for processing and assessment. The baseline biopsy can occur on Day 0 or at any time during the screening period provided the subject has met all other entry criteria prior. After an interim analysis, dependent on data, the biopsy may no longer be a mandatory requirement.

*Change to:*

The salivary gland biopsy surgical technique ~~will be~~ is described in the SRM ~~and training~~. Training reference materials will be provided to site personnel who will perform this procedure.

Biopsy tissue will be shipped to a central histopathology laboratory for processing and assessment. The baseline biopsy can occur on Day 0 or at any time during the screening period provided the subject has met all other entry criteria prior. After ~~the an~~ interim analysis, dependent on data, the biopsy may no longer be a mandatory requirement.

**Efficacy (Section 7.3)****Salivary gland biopsy:***Change from:*

The salivary gland biopsy surgical technique will be described in the SRM and training. Training reference materials will be provided to site personnel who will perform this procedure.

*Change to:*

The salivary gland biopsy surgical technique ~~will be~~ is described in the SRM ~~and training~~. Training reference materials will be provided to site personnel who will perform this procedure.

**Patient Reported Outcomes Assessments (Section 7.3.1)***Change from:*

**PtGA:** the Patient Global Assessment is a patient reported visual analogue scale that provides an overall measure of disease severity. The assessment instrument and technique for administration will be described in the SRM.

*Change to:*

**PtGA:** the Patient Global Assessment is a patient reported ~~visual-analogue~~ **numeric rating** scale that provides an overall measure of disease severity. The assessment instrument and technique for administration will be described in the SRM.

#### **Safety (Section 7.4)**

##### **Adverse Events of Special Interest (Section 7.4.1.4)**

*Change from:*

Adverse events of special interest are malignancies, post-injection systemic reactions, infections, depression/suicidality/self-injury, and deaths. Please refer to Section . The analyses of these events will be described in the Reporting and Analysis Plan.

*Change to:*

**A number of adverse events of special interest have been identified as part of the risk assessment outlined in Section 4.7.1 due to the co-administration of two biologics.and will be monitored for the duration of the study. These AESIs include infections (including opportunistic), systemic infusion / injection reactions, hypersensitivity reactions, malignancy, psychiatric events (including suicidality), severe skin reactions (including Toxic Epidermal Necrolysis and Stevens-Johnson syndrome), immunogenicity, cardiac disorders, posterior reversible encephalopathy syndrome (PRES), PML, and AE's related to the biopsy procedure. The analyses of these events will be described in the Reporting and AnalysisPlan.**

##### **Pregnancy (Section 7.4.2)**

Final bullet point:

*Change from:*

- Women who become pregnant while on active treatment will be withdrawn from therapy but will continue in the trial for safety reporting and outcomes assessments. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

*Change to:*

- Women who become pregnant while on active treatment will be withdrawn from therapy but will continue in the trial for safety reporting and outcomes assessments. The pregnancy must be followed up to determine outcome (including premature termination), and status of mother and child **including a one-year pediatric follow-up.**



**Electrocardiogram (Section 7.4.5)**

*Change from:*

- Triplicate 12-lead ECGs will be obtained at screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

*Change to:*

- ~~Triplicate~~ 12-lead ECGs will be obtained at screening ~~using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.~~ **If the ECG demonstrates a QTcB or QTcF interval  $\geq 450$  msec ( $\geq 480$  msec for subjects with a Bundle Branch Block), there is a requirement to obtain two additional, consecutive ECGs (for a total of three). The investigator will then average the three QTc (and QT) intervals obtained and document the following from the 1st ECG:**
  - Rate
  - PR interval
  - QRS axis

**Clinical Laboratory Assessments (Section 7.4.6)**

*Delete* “Ig” from Table 1. Ig was included in the original Table in error and is not being measured in this study.

**STATISTICAL CONSIDERATIONS AND DATA ANALYSIS (Section 9)**

Throughout Section 9, “analyses” has been replaced with “analysis”

**Hypothesis and Treatment Comparisons (Section 9.1)**

Paragraph 2.

*Change from:*

If deemed appropriate, to investigate the secondary efficacy and mechanistic endpoints, the following exploratory comparisons may be conducted:

*Change to:*

~~If deemed appropriate, to investigate the s~~Secondary efficacy and mechanistic endpoints **will be investigated**. The following exploratory comparisons may be conducted:

**Interim Analysis (Section 9.3.2)***Change from:*

In line with routine pharmacovigilance, subjects' blinded safety data will be reviewed on an ongoing basis during the study conduct by an internal GSK Safety Review Team (SRT).

Study data will be reviewed in a confidential manner during the trial conduct by an internal GSK Safety Review Committee (iSRC). Reviews may include un-blinded efficacy, pharmacodynamic and safety data. An iSRC charter will detail their activities, including when and which data will be reviewed and how the integrity of the study will be maintained in addition to the iSRC group membership.

Once an appropriate number of subjects have completed their Week 24 assessment, interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24. Appropriate available data will be included in the interim analyses, the results of which will be reviewed by the iSRC. Following interim analyses, a number of actions could be taken: the study will continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 total subjects in the study.

The interim analysis decision making criteria will be outlined in the iSRC Charter, where in parallel with all available safety data the ESSDAI score, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification may be considered.

*Change to:*

In line with routine pharmacovigilance, subjects' blinded safety data will be reviewed on an ongoing basis during the study conduct by an internal GSK Safety Review Team (SRT).

~~Study data will be reviewed in a confidential manner during the trial conduct by an internal GSK Safety Review Committee (iSRC). Reviews may include un-blinded efficacy, pharmacodynamic and safety data. An iSRC charter will detail their activities, including when and which data will be reviewed and how the integrity of the study will be maintained in addition to the iSRC group membership.~~

~~Once an appropriate number of subjects have completed their Week 24 assessment, interim analyses and sample size re-estimation will be conducted to assess the effect of the monotherapy belimumab or co-administration therapy when compared to placebo and rituximab monotherapy at Week 24. Appropriate available data will be included in the interim analyses, the results of which will be reviewed by the iSRC. Following interim analyses, a number of actions could be taken: the study will continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment~~

~~arms may be increased following sample size re-estimation, up to a maximum of 120 total subjects in the study.~~

**An internal GSK Safety Review Committee (iSRC), independent of the study team, will maintain governance of the study and will periodically review all available data in an un-blinded manner with a focus on key safety parameters. A Therapeutic Area (Immuno-Inflammation) Data Assessment Committee (TA DAC), independent of the study team, will periodically review un-blinded efficacy data and at the interim analysis will advise the iSRC on adaptive design changes should such changes be required. An iSRC charter details the activities of these committees, including when and which data will be reviewed, how the integrity of the study will be maintained, and the membership of both committees. Once half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, on an exploratory basis, preliminary efficacy analysis will be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be mandated by the iSRC: the study will continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.**

~~The interim analysis decision-making criteria will be outlined in the iSRC Charter, where in parallel with all available safety data the ESSDAI score, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification may be considered.~~

#### **Final Analysis (Section 9.4.1)**

*Change from:*

In addition to the interim analyses, there will be 2 database locks and hence analyses for this study, corresponding to the primary analysis and the follow-up analysis. The database will be locked for the primary analysis after data through the Week 52 visit (or withdrawal visit for those subjects who withdraw during double-blind treatment) for all subjects have been collected, verified and validated. The second database lock will occur after data through the 16-week generalized follow-up period for all subjects have been collected, verified and validated. All subjects and study site personnel (except the unblinded site pharmacist) will remain blinded until the second database lock.

*Change to:*

In addition to the interim ~~analyses~~**analysis**, there will be ~~2 database locks and hence~~**additional** analyses for this study, corresponding to the primary analysis and the follow-up analyses. The ~~database will be locked for the primary analysis~~ **will occur** after ~~the~~ data through the Week 52 visit (or withdrawal visit for those subjects who withdraw during double-blind treatment) for all subjects have been collected, verified and

validated. The ~~second database lock~~**follow up analyses** will occur after data through the 16-week generalized follow-up period **and IFU periods** for all subjects have been collected, verified and validated. All subjects and study site personnel (except the unblinded site pharmacist) will remain blinded until the ~~second database lock~~**follow up analyses have been completed**.

#### **Primary Analysis (Section 9.4.2)**

2<sup>nd</sup> paragraph:

*Change from:*

All safety evaluations will be based on the safety population. Clinical interpretation will be based upon review and displays of AEs, disease related events, laboratory values and vital signs. The principle consideration in this evaluation will be the investigator-reported relationships of either AEs or laboratory abnormalities to IP.

*Change to:*

All safety evaluations will be based on the safety population. Clinical interpretation will be based upon review and displays of AEs, ~~disease related events~~, laboratory values and vital signs. The principle consideration in this evaluation will be the investigator-reported relationships of either AEs or laboratory abnormalities to IP.

#### **Secondary Analysis (Section 9.4.3)**

4<sup>th</sup> and 5<sup>th</sup> paragraphs:

*Change from:*

The ESSDAI, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification change from baseline scores will be statistically analyzed using a MMRM analysis, comparing the belimumab / rituximab or the belimumab monotherapy arm with placebo at each time point. Similar analyses will also be conducted, if deemed appropriate, comparing each monotherapy arm with placebo. The baseline ESSDAI scores will be investigated as a potential co-variate in the model, if deemed appropriate.

In addition, based on the data that we observe in the study, probabilities of success will be determined. For example, what is the probability that we would observe a certain change in the ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

*Change to:*

The ESSDAI, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification change from baseline scores will be statistically analyzed using a **mixed model repeated measures approach** ~~MMRM analysis~~ comparing **the belimumab monotherapy, rituximab monotherapy and belimumab / rituximab**

~~combination therapy or the belimumab monotherapy arm with placebo at each time point. Similar analyses will also be conducted, if deemed appropriate, comparing each monotherapy arm with placebo. Point estimates and corresponding 95% confidence intervals will be estimated for the comparisons of interest. The baseline ESSDAI scores will be investigated as a potential co-variate in the model, if deemed appropriate. Distributional assumptions underlying the analyses will be assessed. Additional models may be investigated.~~

In addition, based on the data that we observe in the study, probabilities of success **of the combination therapy and belimumab monotherapy** will be determined. For example, what is the probability that we would observe a certain change in the ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

## **STUDY GOVERNANCE CONSIDERATIONS (Section 10)**

### **Regulatory and ethical considerations (Section 10.2)**

*Added:*

- Regulatory Agency review and favorable opinion/approval of the study protocol and substantial amendments.

*Deleted to avoid duplication:*

- ~~Signed informed consent must be obtained for each subject prior to participation in the study~~

### **Review Committees (Section 10.8.1)**

*Change from:*

Section 10.8.1 Internal Safety Review Committee (iSRC)

Study data will be reviewed during trial conduct by an iSRC. Reviews may include un-blinded efficacy, pharmacodynamic, and/or safety data. An iSRC charter will detail their activities, including when and which data will be reviewed and how the integrity of the study will be maintained in addition to the group membership.

*Change to:*

**Section 10.8.1 Internal Safety Review Committee (iSRC) and Therapeutic Area Data Assessment Committee (TA-DAC)**

~~Study data will be reviewed during trial conduct by an iSRC. Reviews may include un-blinded efficacy, pharmacodynamic, and/or safety data. An iSRC charter will detail their activities, including when and which data will be reviewed and how the integrity of the study will be maintained in addition to the group membership~~

An internal GSK Safety Review Committee (iSRC), independent of the study team, will maintain governance of the study and will periodically review all available data in an un-blinded manner with a focus on key safety parameters. A Therapeutic Area (Immuno-Inflammation) Data Assessment Committee (TA DAC), independent of the study team, will periodically review un-blinded efficacy data and at the interim analysis will advise the iSRC on adaptive design changes should such changes be required. An iSRC charter details the activities of these committees, including when and which data will be reviewed, how the integrity of the study will be maintained, and the membership of both committees.

The overall responsibility of the iSRC is to protect the ethical and safety interests of subjects recruited into the study while also protecting the scientific validity of the data. The iSRC has the primary governance role for the study.

## **REFERENCES (Section 11)**

*Added:*

Stohl W, Schwarting A, Okada M, et al. A Randomized, Double-Blind, Placebo-Controlled, 52-Week Study of the Efficacy and Safety of Belimumab Administered Subcutaneously Plus Standard Care to Patients with Systemic Lupus Erythematosus (SLE) [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).

van Assen, S, Agmon-Levin, N, Elkayam, O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70: 414–422.

## **APPENDICES**

### **Appendix 1 – Abbreviations and Trademarks**

*Added:*

TA-DAC	Therapeutic Area – Data Assessment Committee
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**Appendix 8 – Collection of Pregnancy information**

Bullet point 3:

*Change from:*

Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

*Change to:*

Subject will be followed **for 1 year** to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. ~~Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.~~

*Added:*

**Appendix 9: American-European Consensus Group Classification**

**Reference: Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002; 61:554–8.**

**Table 2** Revised international classification criteria for Sjögren's syndrome

- I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
  2. Do you have a recurrent sensation of sand or gravel in the eyes?
  3. Do you use tear substitutes more than 3 times a day?
- II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
  2. Have you had recurrently or persistently swollen salivary glands as an adult?
  3. Do you frequently drink liquids to aid in swallowing dry food?
- III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer's I test, performed without anaesthesia ( $\leq 5$  mm in 5 minutes)
  2. Rose bengal score or other ocular dye score ( $\geq 4$  according to van Bijsterveld's scoring system)
- IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue<sup>18</sup>
- V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow ( $\leq 1.5$  ml in 15 minutes)
  2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts<sup>19</sup>
  3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer<sup>20</sup>
- VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

**Table 3** Revised rules for classification*For primary SS*

In patients without any potentially associated disease, primary SS may be defined as follows:

- a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
- b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
- c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

*For secondary SS*

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

*Exclusion criteria:*

Past head and neck radiation treatment  
Hepatitis C infection  
Acquired immunodeficiency disease (AIDS)  
Pre-existing lymphoma  
Sarcoidosis  
Graft versus host disease  
Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

*Added:*

**Appendix 10 to Appendix 13** have been added. These detail changes made to the protocol in previous country specific amendments and in the current global protocol amendment (version 4).



## **12.14. Appendix 14: Protocol changes in Amendment 5**

### **Amendment 5: global amendment (all sites).**

**Protocol Amendment 05, 11 May 2018**

#### **Summary of Modifications (relative to protocol amendment 4) and Rationale:**

##### **1. Protocol Cover Page**

- Protocol version and Revision Chronology updated in line with amendment 5
- Author list removed as this is no longer part of the current GSK protocol template, furthermore authors are captured on technical approval TMF documentation
- Medical Monitor Contact Details updated in line with GSK team changes

##### **2. Protocol Synopsis (Section 1)**

- Clarification that total subject number is approximate, in line with the rest of the document.
- Text inserted to state that withdrawals may be replaced, in line with the main body of the protocol.
- Clarification of Statistical Methods

##### **3. Study Design (Section 4)**

- Clarification of the purpose of the Interim Analysis
- Text inserted to state that withdrawals may be replaced, in line with the main body of the protocol.
- Clarification around process for replacing subject that withdraw early from treatment

##### **4. Selection of Study Populations (Section 5)**

- CD19+ threshold for exclusion provided in alternative units, to correspond with laboratory reporting.
- Requirements for follow up of subjects withdrawn from treatment updated for consistency with the rest of the protocol

##### **5. Study Treatment (Section 6)**

- Clarification around timing requirements for rituximab/placebo infusion premedication
- Clarification of the definition of “sponsor-open”, allowing designated team members to interpret interim analysis data. Also deleted text to clarify that iSRC and TADAC are unblinded throughout the study duration
- Clarification of “weekly” definition for purposes of belimumab overdose reporting

- Clarification that qd means daily
- 6. Study Assessments and Procedures (Section 7)**
- Clarification in Time and Events Table footnote around timing requirements for rituximab/placebo infusion premedication
  - Clarification in Time and Events Table footnote of requirements for time between first and second rituximab/placebo infusions
  - Clarification that central lab will conduct TB screening for subjects in Argentina
- 7. Statistical Considerations and Data Analyses (Section 9)**
- Clarification of statistical methods
- 8. References (Section 11)**
- Correction of publication date
  - Removal and replacement of a publication reference that has been updated

**Protocol Amendment 05: Modifications in detail:**

**PROTOCOL COVER PAGE**

*Add:*

Protocol Amendment Number: 05

*Remove author list:*

**Author (s):** <sup>PPD</sup>

*Updated:*

**Revision Chronology**

GlaxoSmithKline Document Number	Date	Version
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1 for Sweden
Protocol amended in response to comments received from Swedish regulatory authority.		

<b>GlaxoSmithKline Document Number</b>	<b>Date</b>	<b>Version</b>
Local 2014N220285_02	2015-NOV-20	Amendment No. 2 for Norway
Protocol amended in response to comments received from Norwegian regulatory authority.		
Local 2014N220285_03	2016-JAN-04	Amendment No. 3 for Italy
Protocol amended in response to comments received from Italian regulatory authority.		
Global 2014N220285_04	2016-JUN-13	Amendment No. 4
<p>The primary reason for this amendment is to modify the subject selection criteria (specifically exclusion criterion #30 pertaining to exclusionary laboratory thresholds) to better align with the intended population characteristics.</p> <p>Other amendments include the following:</p> <ul style="list-style-type: none"> <li>• Greater clarity is provided regarding the committees involved in monitoring subject safety and review of study data as well as the governance of the study.</li> <li>• It has been made clear that a single formal interim analysis is planned.</li> <li>• The subject withdrawal and study stopping criteria have been modified.</li> <li>• Greater detail is provided regarding prohibited and permitted medications.</li> <li>• Additional guidance is provided regarding vaccination.</li> <li>• Guidance has been provided for tuberculosis assessment during the screening period.</li> <li>• The pregnancy section has been modified to clarify the duration of follow up required.</li> </ul> <p>This amendment incorporates country-specific changes required by Regulatory Authorities during prior review. In addition, changes have been made throughout to provide clarity for the conduct of the study and correct typographical errors.</p> <p>All changes made in Amendment 4 are summarized, rationalized and detailed in Appendix 13 (Section 12.13).</p>		

GlaxoSmithKline Document Number	Date	Version
Global 2014N220285_05	2018-MAY-11	Amendment No. 5
The primary reason for this amendment is to clarify the definition of “sponsor open” in Section 6.3, with respect to study blinding. Additional minor clarifications have been made throughout the protocol.		

*Updated:*

**Medical Monitor/SAE Contact Information:**

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor *	PPD	PPD	Mobile: PPD	NA	Stevenage, UNITED KINGDOM
Secondary Medical Monitor*	PPD	PPD	Mobile: PPD	NA	Stevenage, UNITED KINGDOM
SAE contact information	Case Management Group, Global Clinical Safety and Pharmacovigilance (GCSP)	PPD	NA	PPD	NA

\*Medical monitor name and contact information can also be found in the Study Reference Manual

**PROTOCOL SYNOPSIS FOR STUDY 201842 (Section 1)**

**Type and Number of Subjects**

*Change from:*

Adult subjects with symptomatic and systemically active disease as well as evidence of glandular reserve function will be recruited. Initially, there will be a total of 70 subjects randomized with the potential to increase the number of subjects in one or more arms following sample size re-estimation, up to a maximum of 120 recruited into the study. The randomization ratio will vary dependent on the number of treatment arms continuing following the interim analysis

*Change to:*

Adult subjects with symptomatic and systemically active disease as well as evidence of glandular reserve function will be recruited. Initially, ~~there will be a total of~~ approximately 70 subjects will be randomized. **Withdrawn subjects may be replaced, and there is with the potential to further** increase the number of subjects in one or more arms following sample size re-estimation, up to a maximum of 120 recruited into the study. The randomization ratio will vary dependent on the number of treatment arms continuing following the interim analysis

## **Analysis**

*Change from*

### **Hypotheses and Treatment Comparisons:**

If deemed appropriate, these exploratory comparisons will be made investigating ESSDAI score, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification. For all other parameters, no formal statistical comparisons will be made, although trends over time will be investigated across all treatment arms.

*Change to*

### **Hypotheses and Treatment Comparisons:**

If deemed appropriate, these exploratory comparisons will be made investigating ESSDAI score, stimulated salivary flow, oral dryness numeric response scale and **a subset of salivary gland histology assessments and** B cell quantification. For all other parameters, no formal statistical comparisons will be made, although trends over time will be investigated across all treatment arms.

*Change from*

**Interim Analysis:** Once half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy analysis will be conducted. to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be taken: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study

*Change to*

**Interim Analysis:** Once half of the planned subjects (i.e.: approximately 35 subjects) have completed their Week 24 assessments, a formal interim analysis will take place. Appropriate available safety and efficacy data will be included in the interim analysis. The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy analysis ~~will~~**may** be conducted. to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be taken: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study

*Change from*

**Data Analysis Considerations:** All data will be descriptively summarized, graphically presented and listed appropriately. The relationship between the mechanistic endpoints (e.g., salivary gland B cell quantification) and clinical effects (e.g., ESSDAI score) will be graphically presented and analyzed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the clinical endpoints (e.g., ESSDAI score). This may be conducted through comparing statistical models, incorporating different explanatory terms (i.e., mechanistic endpoints) with the ‘null’ model (no mechanistic endpoints); or, if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed. Comparisons between treatment groups will be conducted if deemed appropriate. For example, the change from baseline in ESSDAI score will be statistically analyzed using a mixed effect model repeated measurement (MMRM) analysis comparing the co-administration with placebo at each time point. Similar analyses may be conducted for other secondary endpoints. In addition, based on the data that we observe in the study, probabilities of success ~~will~~ may be determined, for example, what is the probability that we would observe a certain change in ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

*Change to*

**Data Analysis Considerations:** All data will be descriptively summarized, graphically presented and listed appropriately. The relationship between the mechanistic endpoints (e.g., salivary gland B cell quantification) and clinical effects (e.g., ESSDAI score) will be graphically presented ~~and analyzed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the clinical endpoints (e.g., ESSDAI score). This may be conducted through comparing statistical models, incorporating different explanatory terms (i.e., mechanistic endpoints) with the ‘null’ model (no mechanistic endpoints); or, if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints.~~ The consistency in the changes over time between the endpoints will also be assessed **and further exploratory analyses to**

**characterize relationships between endpoints may be conducted.** Comparisons between treatment groups will be conducted if deemed appropriate. For example, the change from baseline in ESSDAI score will be statistically analyzed using a mixed effect model repeated measurement (MMRM) analysis comparing the co-administration with placebo at each time point. Similar analyses may be conducted for other secondary endpoints. In addition, based on the data that we observe in the study, probabilities of success ~~will~~ may be determined, for example, what is the probability that we would observe a certain change in ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

## **STUDY DESIGN (Section 4)**

### **Overall design (Section 4.1)**

*Change from:*

The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy analysis will be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy. Following the interim analysis, a number of actions could be mandated by the iSRC: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.

*Change to:*

The main purpose of the interim analysis is to assess the safety and tolerability of the study drugs. In addition, preliminary efficacy **data will be evaluated.** ~~analysis will be conducted to enable a sample size re-estimation and obtain an initial estimate of the effect size of the co-administration therapy and belimumab monotherapy.~~ Following the interim analysis, a number of actions could be mandated by the iSRC: the study may continue as planned; one or more treatment arms may be dropped; the number of subjects in some or all treatment arms may be increased following sample size re-estimation, up to a maximum of 120 subjects in the study.

### **Treatment arms and duration (Section 4.2)**

*Change from:*

Approximately 70 subjects will be recruited into the study initially. At Day 0, subjects will be randomized 1:2:2:2 to one of the four treatment arms below

*Change to:*

Approximately 70 subjects will be recruited into the study initially. **Withdrawals may be replaced.** At Day 0, subjects will be randomized 1:2:2:2 to one of the four treatment arms below

**Type and number of subjects (Section 4.4)***Change from:*

If subjects prematurely discontinue the study, additional subjects may be randomized and assigned to the next treatment in the randomization schedule at the discretion of the Sponsor in consultation with the investigator.

*Change to:*

**In addition**, if subjects prematurely discontinue the study, additional subjects may be randomized and assigned to the next treatment in the randomization schedule at the discretion of the Sponsor ~~in consultation with the investigator~~.

**SELECTION OF STUDY POPULATIONS AND WITHDRAWAL CRITERIA (Section 5)****Exclusion Criteria (Section 5.2)***Change from:*

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
<p>32. Have an IgA deficiency (IgA level &lt;10 mg/dL).</p> <p>33. Any of the following screening laboratory values:</p> <ul style="list-style-type: none"> <li>• White blood cells (WBC) &lt;2 x 10<sup>9</sup>/L</li> <li>• Neutrophils &lt;1.5 x 10<sup>9</sup>/L</li> <li>• Circulating IgG &lt; 550 mg / dL</li> <li>• Aspartate aminotransferase (AST) &gt;2.0 times the upper limit of normal</li> <li>• Alkaline phosphatase (ALP) &gt;1.5 times the upper limit of normal</li> <li>• Bilirubin &gt;1.5 times the upper limit of normal (unless direct bilirubin fraction is &lt; 35%)</li> <li>• CD19+ B-lymphocyte counts &lt;0.1 x 10<sup>9</sup>/L (applies only to subjects previously exposed to B cell depleting therapies)</li> </ul> <p>34. For <b>FRANCE ONLY</b>, subjects with legal or administrative guardianship (“tutelle” or “curatelle”), or subjects deprived of liberty, or subjects receiving psychiatric care, or subjects hospitalized in an Health and Social Establishment for purposes other than participation in this study.</p>

*Change to:*

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
<p>35. Have an IgA deficiency (IgA level &lt;10 mg/dL).</p> <p>36. Any of the following screening laboratory values:</p>



- White blood cells (WBC)  $<2 \times 10^9/L$
- Neutrophils  $<1.5 \times 10^9/L$
- Circulating IgG  $< 550 \text{ mg / dL}$
- Aspartate aminotransferase (AST)  $>2.0$  times the upper limit of normal
- Alkaline phosphatase (ALP)  $>1.5$  times the upper limit of normal
- Bilirubin  $>1.5$  times the upper limit of normal (unless direct bilirubin fraction is  $< 35\%$ )
- CD19+ B-lymphocyte counts  $<0.1 \times 10^9/L$  ( **$<100$  per CMM**) (applies only to subjects previously exposed to B cell depleting therapies)

37. For **FRANCE ONLY**, subjects with legal or administrative guardianship (“tutelle” or “curatelle”), or subjects deprived of liberty, or subjects receiving psychiatric care, or subjects hospitalized in an Health and Social Establishment for purposes other than participation in this study.

### **Withdrawal/Stopping Criteria (Section 5.4)**

#### **General Criteria**

*Change from:*

Subject discontinues treatment before the Week 8 Visit	Subject discontinues treatment after the Week 8 Visit and before Week 46	Subject discontinues treatment at or after Week 46
<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ An additional telephone call for urine pregnancy results at approximately 52 weeks after the last rituximab/placebo dose</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>

Subject discontinues treatment before the Week 8 Visit	Subject discontinues treatment after the Week 8 Visit and before Week 46	Subject discontinues treatment at or after Week 46
	➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)	

*Change to:*

Subject discontinues treatment before the Week 8 Visit	Subject discontinues treatment after the Week 8 Visit and before Week 46	Subject discontinues treatment at or after Week 46
<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ <b>maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until approximately 52 weeks after the last dose of rituximab/pbo was administered.</b></li> <li><del>➤ An additional telephone call for urine pregnancy results at approximately 52 weeks after the last rituximab/placebo dose</del></li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>➤ General follow-up visit 16 weeks after last dose of IP</li> <li>➤ Monthly telephone calls for urine pregnancy test results, neurological questionnaire, AEs, SAEs, and concomitant medications during the 16-week general follow-up period.</li> <li>➤ Individualized safety follow-up visits every 12 weeks subsequent to the general follow up period (if applicable)</li> </ul>

## **STUDY TREATMNT (Section 6)**

### **Investigation Product and other Study Treatment (Section 6.1)**

#### **Rituximab**

*Change from:*

Rituximab/placebo will be administered intravenously by an experienced healthcare professional under physician supervision, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an oral anti-pyretic and an oral antihistamine, e.g., paracetamol and diphenhydramine (60 minutes prior to rituximab) and intravenous methylprednisolone (100 mg) (30 minutes prior to rituximab), will be given before each administration of rituximab/placebo.

*Change to:*

Rituximab/placebo will be administered intravenously by an experienced healthcare professional under physician supervision, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an oral anti-pyretic and an oral antihistamine, e.g., paracetamol and diphenhydramine (**approximately 60** minutes prior to rituximab) and intravenous methylprednisolone (100 mg) (**at least 30** minutes prior to rituximab), will be given before each administration of rituximab/placebo.

#### **Blinding (Section 6.3)**

*Change from:*

- Sponsor open refers only to those members of the iSRC and the TA DAC who are unblinded for the interim analysis, as outlined in the iSRC charter. The GSK study team will be blinded except for team members required for monitoring the pharmacy e.g., unblinded monitor etc.

*Change to:*

- Sponsor open refers ~~only~~ to those members of the iSRC and the TA DAC who are unblinded ~~for the interim analysis~~, as outlined in the iSRC charter. The GSK study team will be blinded except for ~~those team members required for monitoring the pharmacy e.g., unblinded monitor etc,~~ **as well as a restricted number of team members required for interpretation of data at the interim analysis, as specified in the iSRC Charter.**

#### **Treatment of study overdose (6.7)**

*Change from:*

For this study, any dose of subcutaneous belimumab in excess of 200 mg per week will be considered an overdose. GSK does not recommend specific treatment for an overdose.

*Change to:*

For this study, any dose of subcutaneous belimumab in excess of 200 mg per week (**7 ± 2 days**) will be considered an overdose. GSK does not recommend specific treatment for an overdose.

### **Treatment after the end of the study (Section 6.8)**

#### **Permitted medications and non-drug therapy**

*Change from:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than 400 mg po qd for 30 days prior to Day 0 and continues this dose for the duration of the study).

*Change to:*

- Hydroxychloroquine (provided subject is on a stable regimen no greater than 400 mg po qd (**ie daily**) for 30 days prior to Day 0 and continues this dose for the duration of the study).

### **STUDY ASSESSMENTS AND PROCEDURES (Section 7)**

#### **Time and events table (Section 7.1)**

#### **Footnotes:**

*Change from:*

8. Both doses of rituximab/placebo will be administered in the clinic. 60 minutes prior to rituximab/placebo, subjects will receive orally an antipyretic and an antihistamine. 30-60 minutes prior to administration of rituximab/placebo, subjects will receive IV 100mg methylprednisilone .The 2nd rituximab/placebo administration at the Week10 visit must be given 14 after the first administration (given at the Week 8 visit). A patient alert card should be sent home with the subject following each dose of rituximab/placebo.

*Change to:*

8. Both doses of rituximab/placebo will be administered in the clinic. **Approximately** 60 minutes prior to rituximab/placebo, subjects will receive orally an antipyretic and an antihistamine. **At least 30-60** minutes prior to administration of rituximab/placebo, subjects will receive IV 100mg methylprednisilone .The 2nd rituximab/placebo administration at the Week10 visit must be given 14 days (**13-18 days, see SRM**) after the first administration (given at the Week 8 visit). A patient alert card should be sent home with the subject following each dose of rituximab/placebo.

### **Screening and Critical Baseline Assessments (Section 7.2)**

*Change from:*

**Tuberculosis:** Assessment of TB in the screening period is to be done via evaluation of the subject's history, physical examination of the subject and, if judged necessary by the Investigator, local laboratory (screening and confirmatory) testing.

*Change to:*

**Tuberculosis:** Assessment of TB in the screening period is to be done via evaluation of the subject's history, physical examination of the subject and, if judged necessary by the Investigator, local laboratory (~~screening and confirmatory~~) testing. **For subjects in Argentina only, the central lab will perform Quantiferon Gold testing.**

## **STATISTICAL CONSIDERATIONS AND DATA ANALYSES (Section 9)**

### **Hypotheses and Treatment Comparisons (Section 9.1)**

*Change from:*

If deemed appropriate, these exploratory comparisons will be made investigating ESSDAI, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification.

*Change to:*

If deemed appropriate, these exploratory comparisons will be made investigating ESSDAI, stimulated salivary flow, oral dryness numeric response scale and **a subset of** salivary gland and **plasma B** cell parameters ~~quantification~~. **Full details will be included in the RAP.**

### **Sample Size Considerations (Section 9.2)**

#### **Sample Size Re-estimation**

*Change from:*

At the interim analysis, the sample size will be re-estimated based on the emerging data from the study. The sample size may need to be re-estimated if higher variability or differing placebo means are observed with any of the four key secondary endpoints (ESSDAI score, stimulated salivary flow, oral dryness NRS or the B cell quantification within salivary gland biopsy); also if treatment arms are dropped from the study. Therefore, any significant deviation from the assumptions used to design the study may result in changes to the number of subjects to be randomized. Further details will be included in the RAP. A maximum of 120 subjects will be recruited into the study.

*Change to:*

At the interim analysis, the sample size ~~will~~ **may** be re-estimated based on the emerging data from the study. The sample size may need to be re-estimated if higher variability or differing placebo means are observed ~~for the with any of the four~~ **ESSDAI, a key** secondary endpoint ~~(ESSDAI score, stimulated salivary flow, oral dryness NRS or the B cell quantification within salivary gland biopsy); also if treatment arms are dropped from the study.~~ Therefore, any significant deviation from the assumptions used to design the study may result in changes to the number of subjects to be randomized. Further details

will be included in the RAP **and guidance document for interim decision making**. A maximum of 120 subjects will be recruited into the study.

## Secondary Analysis

### *Change from:*

All data will be descriptively summarized, graphically presented and listed appropriately.

Each endpoint will be considered individually and at the treatment level where comparisons between treatment groups would be made on any changes observed.

The relationship between the mechanistic (e.g., salivary gland B cell quantification) and clinical effects (e.g., ESSDAI score) will be graphically presented and analyzed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the clinical endpoints (e.g., ESSDAI score). This may be conducted through comparing statistical models; incorporating different explanatory terms (i.e., mechanistic endpoints) with the 'null' model (no mechanistic endpoints); or, if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed.

The ESSDAI, stimulated salivary flow, oral dryness numeric response scale and salivary gland B cell quantification change from baseline scores will be statistically analyzed using a mixed model repeated measures approach when comparing the belimumab monotherapy, rituximab monotherapy and belimumab / rituximab combination therapy with placebo at each time point. Point estimates and corresponding 95% confidence intervals will be estimated for the comparisons of interest. Distributional assumptions underlying the analyses will be assessed. Additional models may be investigated.

In addition, based on the data that we observe in the study, probabilities of success of the co-administration therapy and belimumab monotherapy will be determined. For example, what is the probability that we would observe a certain change in the ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

Further details regarding the statistical analysis will be outlined in the RAP.

### *Change to:*

All data will be descriptively summarized, graphically presented and listed appropriately.

Each endpoint will be considered individually and at the treatment level where comparisons between treatment groups would be made on any changes observed.

The relationship between the mechanistic (e.g., salivary gland B cell quantification) and clinical effects (e.g., ESSDAI score) will be graphically presented ~~and analyzed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the clinical~~

endpoints (e.g., ESSDAI score). This may be conducted through comparing statistical models; incorporating different explanatory terms (i.e., mechanistic endpoints) with the ‘null’ model (no mechanistic endpoints); or, if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed **and further exploratory analyses to characterise relationships between endpoints may be conducted.**

The ESSDAI, stimulated salivary flow **and** oral dryness numeric response scale **and** ~~salivary gland B cell quantification~~ change from baseline scores will be statistically analyzed using a mixed model repeated measures approach ~~when comparing the belimumab monotherapy, rituximab monotherapy and belimumab / rituximab combination therapy with placebo at each time point.~~ Point estimates and corresponding 95% confidence intervals will be estimated for **all** the comparisons of interest **(see Section 9.1) at weeks 24 and 52.** Distributional assumptions underlying the analyses will be assessed. Additional models may be investigated.

**Non-parametric statistical analyses will also be conducted to assess the comparisons of interest for a subset of salivary gland histology assessments, and B cell quantification in plasma. These analyses will be described in the RAP.**

In addition, based on the data that we observe in the study, probabilities of success of the co-administration therapy and belimumab monotherapy ~~may will~~ be determined. For example, what is the probability that we would observe a certain change in the ESSDAI score (i.e., comparator rate), based on the data that we have observed in the study?

Further details regarding the statistical analysis will be outlined in the RAP.

## **REFERENCES (Section 11)**

*Correction made:*

Mariette X, Seror R, Quartuccio L, et al. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis* 2013; 74: 526-31.

*Subsequently, the reference has been updated throughout the document.*

*Removed:*

Stohl W, Schwarting A, Okada M, et al. A Randomized, Double-Blind, Placebo-Controlled, 52-Week Study of the Efficacy and Safety of Belimumab Administered Subcutaneously Plus Standard Care to Patients with Systemic Lupus Erythematosus (SLE) [abstract]. *Arthritis Rheumatol.* 2015; 67 (suppl 10).

*Added:*

**Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a**

**fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol. 2017;69(5):1016-1027.**

*Subsequently, the reference has been updated throughout the document.*

## **APPENDICES (Section 12)**

### **Appendix 1 – Abbreviations and Trademarks**

*Added:*

CMM	Cubic Millimeter
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## **12.15. Appendix 15: Protocol changes in Amendment 6**

### **Amendment 6: global amendment (all sites).**

**Protocol Amendment 06, 25 June 2019**

#### **Summary of Modifications (relative to protocol amendment 5) and Rationale:**

**1. Protocol Cover Page**

- Protocol version and Revision Chronology updated in line with amendment 6
- Medical Monitor Contact Details updated in line with GSK team changes

**2. Follow up Periods (Section 4.3.2)**

- Clarification of when a subject is not required to enter the Individualised Follow Up period

**3. Blinding (Section 6.3)**

- Clarification of timing of unblinding for GSK staff and site staff

**4. Statistical Considerations and Data Analyses (Section 9)**

- Correction of 4 sub-headers

#### **PROTOCOL COVER PAGE**

*Add:*

Protocol Amendment Number: 06

*Updated:*

**Revision Chronology**

<b>GlaxoSmithKline Document Number</b>	<b>Date</b>	<b>Version</b>
2014N220285_00	2015-JUN-17	Original
Local 2014N220285_01	2015-OCT-15	Amendment No. 1 for Sweden
Protocol amended in response to comments received from Swedish regulatory authority.		
Local 2014N220285_02	2015-NOV-20	Amendment No. 2 for Norway
Protocol amended in response to comments received from Norwegian regulatory authority.		
Local 2014N220285_03	2016-JAN-04	Amendment No. 3 for Italy
Protocol amended in response to comments received from Italian regulatory authority.		
Global 2014N220285_04	2016-JUN-13	Amendment No. 4
<p>The primary reason for this amendment is to modify the subject selection criteria (specifically exclusion criterion #30 pertaining to exclusionary laboratory thresholds) to better align with the intended population characteristics.</p> <p>Other amendments include the following:</p> <ul style="list-style-type: none"> <li>• Greater clarity is provided regarding the committees involved in monitoring subject safety and review of study data as well as the governance of the study.</li> <li>• It has been made clear that a single formal interim analysis is planned.</li> <li>• The subject withdrawal and study stopping criteria have been modified.</li> <li>• Greater detail is provided regarding prohibited and permitted medications.</li> <li>• Additional guidance is provided regarding vaccination.</li> <li>• Guidance has been provided for tuberculosis assessment during the screening period.</li> <li>• The pregnancy section has been modified to clarify the duration of follow up required.</li> </ul>		

GlaxoSmithKline Document Number	Date	Version
<p>This amendment incorporates country-specific changes required by Regulatory Authorities during prior review. In addition, changes have been made throughout to provide clarity for the conduct of the study and correct typographical errors.</p> <p>All changes made in Amendment 4 are summarized, rationalized and detailed in Appendix 13 (Section 12.13).</p>		
Global 2014N220285_05	2018-MAY-11	Amendment No. 5
<p>The primary reason for this amendment is to clarify the definition of “sponsor open” in Section 6.3, with respect to study blinding. Additional minor clarifications have been made throughout the protocol.</p>		
Global 2014N220285_06	2019-JUN-25	Amendment No. 6
<p>The primary reason for this amendment is to clarify the timing of unblinding for GSK staff and site staff. Additional minor updates have been made in several sections of the protocol</p>		

*Updated:*

**Medical Monitor/SAE Contact Information:**

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor *	PPD	PPD	Mobile: PPD	NA	Stevenage, UNITED KINGDOM
Secondary Medical Monitor*	PPD	PPD	Mobile: PPD	NA	Upper Providence US
SAE contact information	Case Management Group, Global Clinical Safety and Pharmacovigilance (GCSP)	PPD	NA	PPD	NA

**\*Medical monitor name and contact information can also be found in the Study Reference Manual**

**STUDY DESIGN (Section 4)****Individualised follow up period (Section 4.3.2)**

*added:*

**Subjects who prior to the Week 68 visit receive a disease modifying therapy that may affect B-cell numbers are not required to enter the IFU.**

**STUDY TREATMENT (Section 6)****Blinding (Section 6.3)**

*Change from:*

This will be a double blind (sponsor open) study and the following will apply:

- All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the subject will be blinded to the treatment allocated to individual subjects.
- The investigator or treating physician may unblind a subject's treatment assignment only in the case of an emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options before unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the eCRF.
- An unblinded pharmacist will be used at each study site to prepare rituximab and its placebo for intravenous administration. Unblinded monitors will be assigned to review all pharmacy records, storage and procedures.
- An unblinded member of staff at each site will be assigned to use the randomization software (RAMOS NG) and to receive all drug shipments and notifications.
- Following discussion with GSK medical monitor, a subject may continue in the study if that subject's treatment assignment is unblinded. The primary reason for unblinding (the event or condition which led to the unblinding) will be recorded in the eCRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- During the treatment and 16-week general follow up phase, all study staff (which includes the investigator, sub-investigators, other site trial staff, the subject, and those managing the conduct of the study) will remain blinded to central laboratory data that have the potential to unblind a subject's treatment assignment. Such data may include but is not necessarily limited to:
  - B-cell lymphocyte counts including results from flow cytometry
  - IgM and IgA levels

Refer to the central laboratory manual for additional information.

- The iSRC will perform safety reviews of laboratory data during the conduct of the study, as outlined within the iSRC charter.
- Sponsor open refers to those members of the iSRC and the TA DAC who are unblinded, as outlined in the iSRC charter. The GSK study team will be blinded except for those monitoring the pharmacy e.g., unblinded monitor etc, as well as a restricted number of team members required for interpretation of data at the interim analysis, as specified in the iSRC Charter

*Change to:*

This will be a double blind (sponsor open) study and the following will apply:

- All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the subject will be blinded to the treatment allocated to individual subjects **until the primary and follow up analyses have been completed (see Section 9.4.1).**
- The investigator or treating physician may unblind a subject's treatment assignment only in the case of an emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options before unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.

- The date and reason for the unblinding must be fully documented in the eCRF.
- An unblinded pharmacist will be used at each study site to prepare rituximab and its placebo for intravenous administration. Unblinded monitors will be assigned to review all pharmacy records, storage and procedures.
- An unblinded member of staff at each site will be assigned to use the randomization software (RAMOS NG) and to receive all drug shipments and notifications.
- Following discussion with GSK medical monitor, a subject may continue in the study if that subject's treatment assignment is unblinded. The primary reason for unblinding (the event or condition which led to the unblinding) will be recorded in the eCRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- During the treatment and ~~16-week general follow up~~ **phases (see Sections 4.3.1 and 4.3.2)**, all study staff (which includes the investigator, sub-investigators, other site trial staff, **and** the subject ~~and those managing the conduct of the study~~) will remain blinded to central laboratory data that have the potential to unblind a subject's treatment assignment. Such data may include but is not necessarily limited to:
  - B-cell lymphocyte counts including results from flow cytometry
  - IgM and IgA levels

Refer to the central laboratory manual for additional information.

- The iSRC will perform safety reviews of laboratory data during the conduct of the study, as outlined within the iSRC charter.
- Sponsor open refers to those members of the iSRC and the TA DAC who are unblinded, as outlined in the iSRC charter. The GSK study team will ~~be~~ **remain** blinded **until the primary analysis (see Section 9.4.1)** except for those ~~monitoring the pharmacy~~ **in unblinded roles** e.g., unblinded monitor for **monitoring the pharmacy** etc, as well as a restricted number of team members required for interpretation of data at the interim analysis (**Section 9.3.2**), as specified in the iSRC Charter.

## **STATISTICAL CONSIDERATIONS AND DATA ANALYSES (Section 9)**

### **Key Elements of Analysis Plan (Section 9.4)**

#### **Change from:**

#### **9.4.1 Final Analysis**

**Change to:****9.4.1 ~~Final~~ Primary Analysis and Follow up Analysis****Change from:****9.4.2 Primary Analyses****Change to:****9.4.2 Primary Analyses Analysis of Primary Endpoints****Change from:****9.4.3 Secondary Analyses****Change to:****9.4.3 Secondary Analysis Analysis of Secondary Endpoints****Change from:****9.4.4 - Other Analyses****Change to:****9.4.4 - Analysis of Other Analyses Endpoints**