TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Pilot Study to Evaluate Molecular Imaging Methods in Primary Sjogren's Syndrome

Compound Number: None

Development Phase: NA

Effective Date: 24-MAY-2017

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N227551_00	2016-JUN-13	Original
2015N227551_01	2017-MAY-24	Amendment No. 1

- Updates to some T&E windows (pregnancy tests, V1 for FRP and minor salivary gland biopsy)
- Flexibility to allow follow up for pSS subjects by telephone.
- Updates to blood tests as per file notes issued during study.
- Typographical error in Section 9.2 changed from “within approximately 0.62 of the point estimate” to “within approximately 0.64 of the point estimate”.
- Minor formatting changes

SPONSOR SIGNATORY

PPD

24th May 2017

Caroline Savage
VP & Head Experimental Medicine Unit
Immunoinflammation Therapy Area

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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	Dr PPD PPD	Tel: PPD Mobile: PPD PPD	Mobile: PPD PPD PPD	PPD	GSK Medicines Research Centre, Gunnels Wood, Stevenage, Hertfordshire, SG1 2NY, UK
Secondary Medical Monitor	Dr PPD PPD	Tel: PPD PPD	Mobile: PPD PPD		
SAE contact information	[Medical monitor as above]				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

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): NA

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 203818

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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 203818

Rationale

This is a pilot imaging study designed to assess whether molecular imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), ^{11}C-Methionine (MET) PET/CT and salivary gland magnetic resonance imaging (MRI) have the potential to characterize and quantify disease manifestations in primary Sjögren's syndrome (pSS) subjects. This will be achieved by assessing the associations and consistency between the imaging techniques studied, clinical assessments (salivary and tear flow and clinical scores), laboratory biomarkers and histological findings on minor salivary gland biopsy. It is hoped that the methodologies may help with the selection of subjects, and/or assessments of treatment response in future clinical studies. For example, subjects with on-going inflammation and a degree of gland function might be more suitable for anti-inflammatory therapies.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the use of ^{18}F-FDG PET/CT in assessing increased glucose uptake as a biomarker of inflammation in pSS subjects.	• Semi-quantitative parameters of uptake in selected body areas, including salivary glands for ^{18}F-FDG: – Standardised uptake value (SUV) – Tissue-to-reference ratio – Total inflammatory volume (TIV) where anatomically relevant.
• To investigate the use of ^{11}C-Methionine (MET) PET/CT in assessing salivary glandular function in pSS subjects and healthy volunteers.	• Semi-quantitative parameters of uptake in selected areas, including salivary glands for ^{11}C-MET: – SUV – Tissue-to-reference ratio – TIV where anatomically relevant.
• To investigate the use of multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including: exchange rate (K_{trans}), apparent diffusion coefficient (ADC), pure diffusion coefficient (D) and microvascular volume fraction (f) as data permits.

Objectives	Endpoints
Secondary	
• To characterize the pharmacokinetics of ^{11}C-MET PET tracer *in vivo* to allow static imaging parameters to be verified.	• Generation of quantitative outcome parameters (rate of ^{11}C-MET accumulation, as data permits) using a full quantitative analysis of dynamic PET scans. • Comparison of static and dynamic imaging metrics in ^{11}C-MET.
Exploratory	
• To explore the use of novel multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including: initial rate of enhancement (IRE), maximal signal intensity enhancement (ME), lipid content, T1 relaxation, and volume, as data permits.
• To explore the associations of the salivary gland imaging parameters with clinical and histological parameters of salivary glands.	• Association between ^{18}F-FDG PET/CT (pSS subjects only), ^{11}C-MET PET/CT and MRI parameters (healthy volunteers and pSS subjects) in the region of the salivary glands with each other and with clinical measures including: – Basal and stimulated salivary flow – Histological scores from minor salivary gland biopsies including but not limited to lymphocyte count and focus score (pSS subjects) – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) – European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), in particular subcomponents relevant to salivary gland function (pSS subjects).

Objectives	Endpoints
• To explore the extent of non-salivary gland (systemic) abnormalities detected on ^{18}F-FDG PET/CT and ^{11}C-MET PET/CT, and the association of these abnormalities with clinical scores/relevant sub-scores and laboratory biomarkers in pSS subjects.	• Semi-quantitative parameters in selected areas systemically for ^{18}F-FDG and ^{11}C-MET (including but not limited to lymph nodes, thyroid, lacrimal glands, lungs and pancreas) and the associations of these parameters with: – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) – Lacrimal gland function as measured by Schirmer's test – ESSDAI and ESSPRI and organ-specific subcomponents relating to the area imaged, where available.
• To compare the metabolomic profiles of pSS subjects and healthy volunteers, to assess the intra-individual variability of the metabolome over time, and the ability of samples from different bodily sites to discriminate pSS subjects from healthy volunteers.	• Compare the metabolome/proteome of pSS subjects with healthy volunteers. • Assess the variability in the metabolome and/or proteomic profile of individual subjects taken at 2 separate time points (Baseline and Visit 2). • Compare the metabolome and/or proteomic profile from different body fluids/sites, and their utility in distinguishing pSS subjects from healthy volunteers. • Samples collected will be saliva, tears and plasma.

Overall Design

Healthy volunteers will be enrolled in Group A and pSS subjects will be enrolled in Group B.

The subjects will be required to attend the clinical unit for a Screening/Baseline visit, an imaging visit (Visit 1) a sample collection visit (Visit 2) and a Follow up. The pSS subjects will have a minor salivary gland biopsy at Visit 2. Females of reproductive potential (FRP) will be required to have a negative pregnancy test as determined by serum hCG test at screening and will be required to have a negative urine pregnancy test

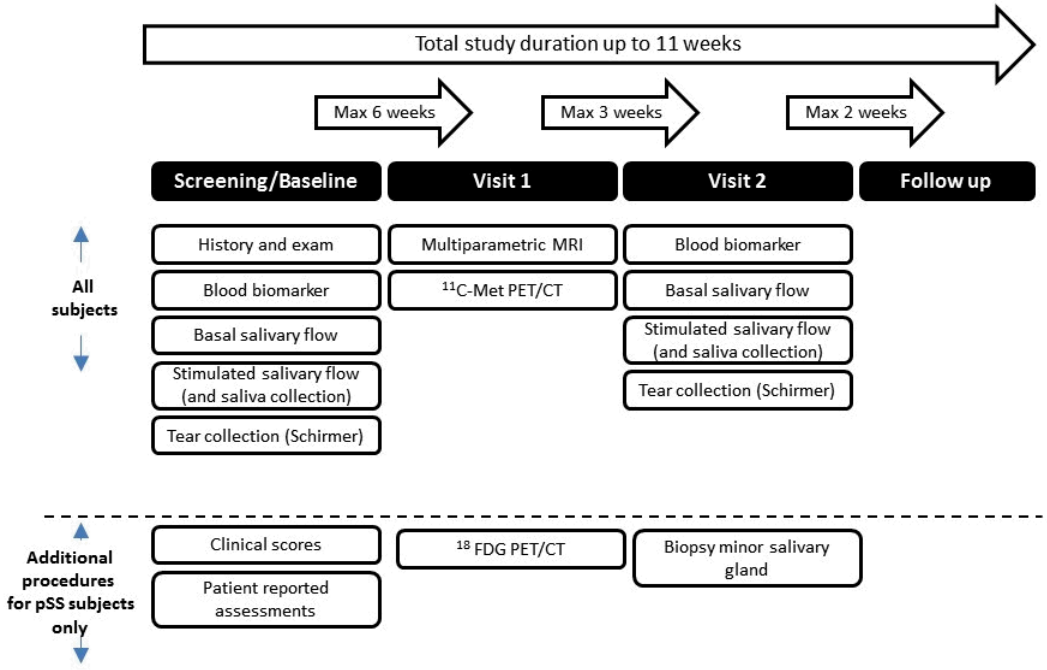
3-8 days prior to Visit 1, and on Visit 1. If Visit 1 is split over more than 1 day there must be a negative urine pregnancy test on each day, prior to scanning.

All procedures will be performed as outpatient visits.

No investigational medicinal product (IMP) will be administered to subjects enrolled in this study.

Treatment Arms and Duration

Subject Participation Flow



Both groups will undergo a Screening/Baseline visit where they will have measurement of basal and stimulated, salivary flow rate (including saliva collection), Schirmer's test and blood samples for biomarkers. The pSS subjects will also have additional clinical scores and patient reported assessments.

Subjects who have completed the screening/baseline will return for an imaging visit (Visit 1). The imaging visit should occur within 6 weeks (42 days) after the screening visit . The following imaging procedures will be performed:

- Group A (healthy volunteers) will undergo an MRI of the salivary glands and ^{11}C-MET PET/CT (dynamic scan of the salivary glands followed by head to hip static scan).

- Group B (pSS subjects) will undergo an MRI of the salivary glands, ^{11}C-MET PET/CT (as for Group A) and ^{18}F-FDG PET/CT (static scan head to hip).

Visit 2 will occur within 3 weeks after Visit 1. Visit 2 will involve measurement of basal and stimulated (chewing paraffin) salivary flow rate (including saliva collection), Schirmer's test (including tear collection), blood samples for biomarkers (metabolomics/proteomics). In addition a minor salivary gland biopsy will be performed on the pSS subjects (Group B). If it is not possible, for logistical or other reasons to schedule the minor salivary gland biopsy within 3 weeks of Visit 1, then this part of Visit 2 may be performed up to 6 weeks after Visit 1, with the prior agreement of the medical monitor.

There will be a Follow up visit within 2 weeks of Visit 2. This may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) may have their Follow up visit conducted in person , or by telephone if the Investigator considers it clinically appropriate. Adverse events (AE) will be reviewed at this visit for all of the subjects (Group A and Group B).

Visit 1 and Visit 2 may be split over more than one day.

The total duration of participation in the study will be a maximum of 11 weeks (up to 14 weeks only if it is necessary to delay the minor salivary gland biopsy), although the visits should be completed sooner if feasible.

Type and Number of Subjects

Between approximately 4 to 12 healthy volunteers and between approximately 8 to 12 pSS subjects will be recruited into the study. As there is very little data about the variability of the imaging parameters, in-stream review of the variability will be conducted in order to determine the number of subjects that are required for PET/CT and/or MRI. In order to minimize radiation exposure to healthy volunteers, a maximum of 8 healthy volunteer subjects will undergo the ^{11}C MET PET/CT scan component.

As pSS affects females in about 90% of cases, and in order to reduce variability, initially only female healthy volunteer subjects will be recruited. If in the course of the study male pSS subjects are recruited, male healthy volunteers may be recruited at the discretion of the Sponsor. The ages of the healthy volunteers will be matched approximately to the ages of the pSS subjects as far as is practically possible, and within the age restrictions of the protocol.

Healthy volunteers and pSS subjects will be recruited simultaneously. However, there may be some staggering in the recruitment of subjects to allow approximate age and sex matching.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor.

Analysis

This is an exploratory study and therefore no formal sample size calculations have been conducted. Sample size is primarily driven by feasibility and knowledge of disease heterogeneity to sufficiently evaluate the primary and supportive secondary objectives of the study.

Descriptive statistics and graphical displays if appropriate will be presented for all ^{18}F-FDG PET/CT derived parameters across the regions of interest (ROI) for all pSS subjects and for all ^{11}C-MET PET/CT and multi-parametric MRI derived parameters across the ROI for all healthy volunteers and pSS subjects. An exploratory comparison of pSS subjects vs healthy volunteers may be performed for each ^{11}C-MET PET/CT and multi-parametric MRI derived quantitative parameter as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval. Descriptive statistics and graphical displays if appropriate will also be presented for all derived parameters from dynamic PET imaging and pharmacokinetic (PK) analyses. If data permits, statistical analyses and/or graphical presentation of radio-PK modelling indices with ^{11}C-MET static imaging matrices will be conducted to assess correlation.

2. INTRODUCTION

2.1. Study Rationale

This pilot study is designed to assess the potential value of imaging methods in pSS subjects. The selected imaging methods will include:

- Positron Emission Tomography (PET) / Computed Tomography (CT) with ^{11}C-Methionine (MET) imaging to characterize protein synthesis within the salivary and other glands as a potential marker of gland function;
- Multi-parametric Magnetic Resonance imaging (MRI) of the salivary glands to assess gland function, structure and potential biomarkers of inflammation; and
- PET/CT with ^{18}F-Fluorodeoxyglucose (FDG) as a marker of inflammation to assess disease extent in the salivary glands and systemically.

The aim of the study is to determine whether the imaging methodologies under investigation have the potential to characterize and quantify disease manifestations in Primary Sjögren's Syndrome (pSS) subjects. This will be achieved by assessing the associations between the imaging techniques studied, clinical assessments (salivary and tear flow and clinical scores), biomarkers (including metabolomics/proteomics) and histological findings on minor salivary gland biopsy. It is hoped that the methodologies may help in subject selection and/or assessment of treatment response in future clinical studies. For example subjects with on-going inflammation, and a degree of gland function might be more suitable for anti-inflammatory therapies.

2.2. Brief Background

Primary Sjögren's Syndrome (pSS) is a chronic systemic disease with a female over male preponderance of 9:1 [Vitali, 2002, Helmick, 2008] that primarily involves the salivary

(xerostomia) and lacrimal (keratoconjunctivitis sicca) glands caused by inflammation [Fox, 2005 and Gomes Pde, 2012]. However, any organ or mucosal surface may be involved, with the risk of lymphoma development remaining the most serious complication [Ziakas, 2014].

There is a need to develop methods that can reduce both the time to diagnosis and assess the effect of current and new therapies in these patients in a more quantitative manner, in particular for assessing the heterogeneous nature of the disease, and selecting patients most likely to respond to therapies (*ie* those with active disease and a degree of gland function). Molecular imaging methods have the potential to provide 3D high resolution, sensitive and quantitative measures of disease manifestations, combined with whole body assessment for the PET methods. This makes them an attractive tool to consider for assessing disease status at entry to clinical studies, and potentially for monitoring treatment effects.

The methods under study are ^{18}F-FDG PET/CT as a measure of inflammation, ^{11}C-MET PET/CT as a measure of protein synthesis within the glands, and multi-parametric MRI to assess both structural and functional changes in salivary glands in pSS. Ultrasonography has been used as a diagnostic tool in pSS, but its role in monitoring treatment effects in multicentre studies is more challenging and less clear.

Published literature around use of ^{18}F-FDG, ^{11}C-MET PET and multi-parametric MRI in pSS is limited as the methods are more commonly used in other indications: ^{18}F-FDG uptake is a marker for increased glucose uptake, which is closely correlated to certain types of metabolism such as that of malignant cells but it is also a feature of inflammation with inflammatory foci exhibiting high ^{18}F-FDG uptake [Bakheet, 1998]. In pSS, the relation of ^{18}F-FDG uptake to inflammation needs to be further explored but a recent report by Ziakas [Ziakas, 2014] showing a strong correlation between inflammation and FDG uptake in Sjögren's patients treated for salivary lymphomas is encouraging [Ziakas, 2014]. In addition, Cohen *et al*. [Cohen, 2013] reviewed the PET data from 32 Sjögren's patients that underwent ^{18}F-FDG PET and showed that ^{18}F-FDG uptake was increased in 75% of patients with 60% displaying increased uptake in lymph nodes, 50% in the parotid glands, 28% in the submandibular glands, 28% in the lung and 6% in the thyroid.

Salivary gland disease is a hallmark for pSS and PET with ^{11}C-MET can potentially assess function with a superior sensitivity and anatomical resolution than the gold standard contrast sialography or salivary gland scintigraphy with ^{99m}Tc-sodium pertechnectate. ^{11}C-MET, a labelled essential amino acid, is most popular for PET imaging of brain tumours; events such as cellular proliferation are associated with increased protein synthesis and hence avid uptake of these precursors [Glaudemans, 2013]. Furthermore, ^{11}C-MET has been used for measuring liver protein synthesis and assessing excretory pancreas function [Harris, 2013]. Dynamic ^{11}C-MET has been used as a quantitative measure of regional gland function in the major salivary glands in head-and-neck cancer patients that underwent loss of salivary gland function as a result of radiotherapy [Buus, 2004]. This study aims to determine whether there is a disturbance in protein synthesis in salivary glands that correlates to disease activity, although the relationship between inflammation and gland function (protein synthesis) in

pSS is as yet unclear. In addition, the ability of PET to image the whole body will also allow recording of function in other glands such as the pancreas.

Magnetic resonance imaging (MRI) offers a superior soft tissue contrast and high resolution to assess anatomical organ changes (using T1 or T2 weighted) *in vivo*, also non-invasively. Furthermore, functional imaging techniques are also available using MRI: Dynamic Contrast Enhanced (DCE)-MRI provides information about the microvasculature of tissues. Since the salivary glands are highly perfused, this technique may be adequate for the evaluation of damage to the vessels in the salivary glands [Houweling, 2011]. Diffusion Weighted (DW)-MRI maps the diffusion process of molecules, mainly water, and yields qualitative and quantitative information reflecting tissue cellularity and cell membrane integrity. The intravoxel incoherent motion (IVIM) model of diffusion may be sensitive to early microstructural changes to the parotid gland in pSS patients [Su, 2015]. It thereby complements the morphological information obtained by conventional MRI. Roberts and colleagues [Roberts, 2008] compared the parotid gland microvascular characteristics in 21 patients with Sjögren's syndrome with those in 11 healthy volunteers. They demonstrated significant differences in DCE parameters with patients also displaying greater gland heterogeneity [Roberts, 2008].

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To investigate the use of ^{18}F-FDG PET/CT in assessing increased glucose uptake as a biomarker of inflammation in pSS subjects.	• Semi-quantitative parameters of uptake in selected body areas, including salivary glands for ^{18}F-FDG in selected areas: – Standardised Uptake Value (SUV) – Tissue-to-reference ratio – Total Inflammatory Volume (TIV) where anatomically relevant.
• To investigate the use of ^{11}C- MET PET/CT in assessing salivary glandular function in pSS subjects and healthy volunteers.	• Semi-quantitative parameters of uptake in selected areas, including salivary glands for ^{11}C-MET : – SUV – Tissue-to-reference ratio – TIV where anatomically relevant.
• To investigate the use of multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including: Exchange rate (K_{trans}), Apparent Diffusion Coefficient (ADC), pure

Objectives	Endpoints
	diffusion coefficient (D) and microvascular volume fraction (f) as data permits.
Secondary	
• To characterize the pharmacokinetics of ^{11}C-MET PET tracer *in vivo* to allow static imaging parameters to be verified.	• Generation of quantitative outcome parameters (rate of ^{11}C-MET accumulation, as data permits) using a full quantitative analysis of dynamic PET scans. • Comparison of static and dynamic imaging metrics in ^{11}C-MET.
Exploratory	
• To explore the use of novel multi parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including, Initial Rate of Enhancement (IRE), maximal signal intensity enhancement (ME), lipid content, T1 relaxation and volume, as data permits.
• To explore the associations of the salivary gland imaging parameters with clinical and histological parameters of salivary glands.	• Association between ^{18}F-FDG PET/CT (pSS subjects only), ^{11}C-MET PET/CT and MRI parameters (healthy volunteers and pSS subjects) in the region of the salivary glands with each other and with clinical measures including: – Basal and stimulated salivary flow – Histological scores from minor salivary gland biopsies including but not limited to lymphocyte count and focus score (pSS subjects) – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) • European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), in particular

Objectives	Endpoints
	subcomponents relevant to salivary gland function (pSS subjects).
• To explore the extent of non-salivary gland (systemic) abnormalities detected on ^{18}F-FDG PET/CT and ^{11}C-MET PET/CT, and the association of these abnormalities with clinical scores/relevant sub-scores and laboratory biomarkers in pSS subjects.	• Semi-quantitative parameters in selected areas systemically for ^{18}F-FDG and ^{11}C-MET (including but not limited to lymph nodes, thyroid, lacrimal glands, lungs and pancreas) and the associations of these parameters with: – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) – Lacrimal gland function as measured by Schirmer's test – ESSDAI and ESSPRI and organ-specific subcomponents relating to the area imaged, where available.
• To compare the metabolomic profiles of pSS subjects and healthy volunteers, to assess the intra-individual variability of the metabolome over time, and the ability of samples from different bodily sites to discriminate pSS subjects from healthy volunteers.	• Compare the metabolome/proteome of pSS subjects with healthy volunteers. • Assess the variability in the metabolome and/or proteomic profile of individual subjects taken at 2 separate time points (Baseline and Visit 2). • Compare the metabolome and/or proteomic profile from different body fluids/sites, and their utility in distinguishing pSS subjects from healthy volunteers. • Samples collected will be saliva, tears and plasma.

4. STUDY DESIGN

4.1. Overall Design

Healthy volunteers will be enrolled in Group A and pSS subjects will be enrolled in Group B.

The subjects will be required to attend the clinical unit for a Screening/Baseline visit, an imaging visit (Visit 1) a sample collection visit (Visit 2) and a Follow up visit.

If Females of Reproductive Potential (FRP) are included they must have a negative pregnancy test as determined by serum human chorionic gonadotropin (hCG) test at screening, and a negative urine pregnancy test 3-8 days prior to Visit 1, and on Visit 1. If Visit 1 is split over more than 1 day there must be a negative urine pregnancy test on each day, prior to scanning.

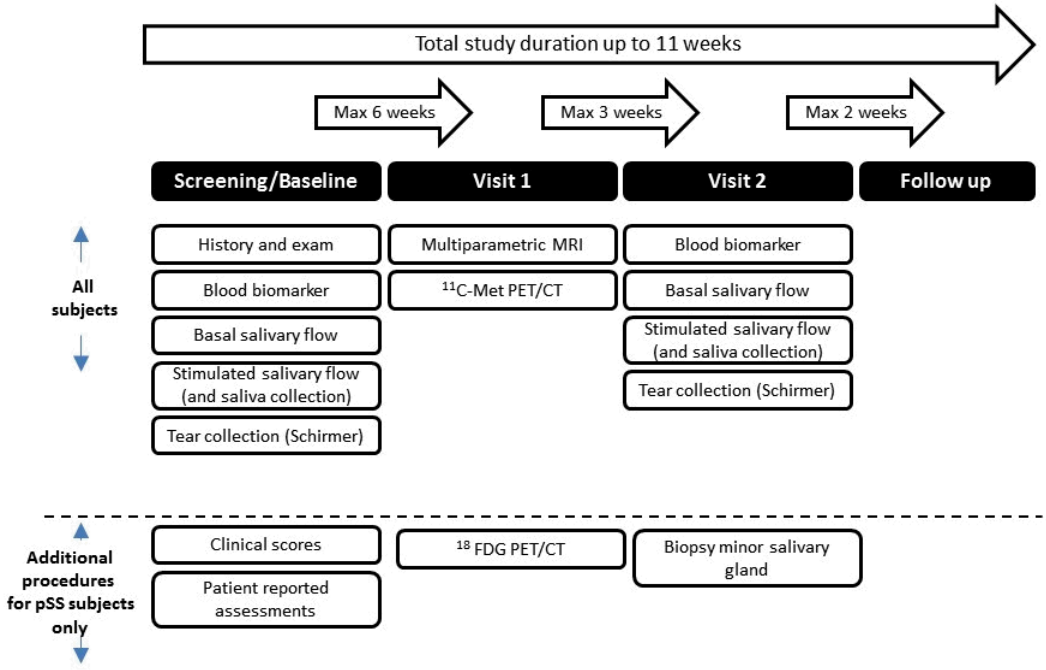
The follow up may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) may have their Follow up visit conducted in person, or by telephone if the Investigator considers it clinically appropriate.

All assessments will be done as outpatient visits.

No investigational medicinal product (IMP) will be administered to subjects enrolled in this study.

4.2. Treatment Arms and Duration

Figure 1 Study Schematic



Screening/Baseline

Both groups of subjects will undergo a Screening/Baseline visit. At this visit, following the subject providing written consent to be enrolled on the study, the eligibility of the subjects will be assessed and baseline assessments will be performed (See Time and Events tables, Section 7.1.).

Visits

Subjects who have completed the Screening/Baseline and are eligible for the study will have an imaging visit (Visit 1).

- Group A (healthy volunteers) will undergo an MRI of the salivary glands and ^{11}C-MET PET/CT (dynamic scan of the salivary glands followed by head to hip static scan).
- Group B (pSS subjects) will undergo an MRI of the salivary glands, ^{11}C-MET PET/CT (as for Group A) and ^{18}F-FDG PET/CT (static head to hip scan).

Visit 2 will occur within 3 weeks after the completion of the assessments performed at Visit 1. The assessments will include vital signs measurement, pregnancy test (FRP only), plasma collection for the measurement of metabolomics/proteomics, measurement of basal and stimulated (chewing paraffin) salivary flow rate (including saliva collection) and Schirmer's test (including tear collection). Concomitant medication and adverse event details will be recorded.

In addition, a minor salivary gland biopsy will be performed on the pSS subjects (Group B). If it is not possible, for logistical or other reasons to schedule the minor salivary gland biopsy within 3 weeks of Visit 1, then this part of Visit 2 may be performed up to 6 weeks after Visit 1, with the prior agreement of the medical monitor.

Visit 1 and Visit 2 may be split over more than one day. The total duration of participation in the study will be a maximum of 11 weeks (14 only if it becomes necessary to delay the minor salivary gland biopsy), although the visits should be completed sooner if feasible.

The details of the samples to be collected and the procedures to be performed are included in Section 7.

Follow up

Within 2 weeks of Visit 2 there will be a follow up visit. This may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) may have their Follow up visit in person, or by telephone if the Investigator considers it clinically appropriate. Adverse events (AE) will be reviewed at this visit for all of the subjects (Group A and Group B)

The total duration of the study will be up to 11 weeks (14 only if it becomes necessary to delay the minor salivary gland biopsy), although ideally the study should be completed as soon as practicable within the time windows.

4.3. Type and Number of Subjects

Between approximately 4 to 12 healthy volunteers, and between approximately 8 to 12 pSS subjects will be recruited into the study. As there is very little data about the variability of the imaging parameters, in-stream review of the variability of PET/CT and MRI data will be conducted in order to determine the number of subjects that are required for PET/CT and/or MRI (see Section 9.2.2). In order to minimize radiation exposure to healthy volunteers, a maximum of 8 healthy volunteer subjects will undergo the ^{11}C-MET PET/CT scan component.

As pSS affects females in about 90% of cases, and in order to reduce variability, initially only female healthy volunteer subjects will be recruited. If in the course of the study male pSS subjects are recruited, male healthy volunteers may be recruited at the discretion of the Sponsor. The ages of the healthy volunteers will be matched approximately to the ages of the pSS subjects as far as is practically possible, and within the age restrictions of the protocol. The procedure for approximate age matching will be described in the Study Reference Manual (SRM).

Healthy volunteers and pSS subjects will be recruited simultaneously. However, there may be some staggering in the recruitment of subjects to allow approximate age and sex matching.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor.

4.4. Design Justification

An ^{18}F-FDG-PET/CT is being used as a biomarker of inflammation to assess disease extent systemically. As ^{18}F-FDG is well characterized as a tracer, there is no need in this study to carry out this investigation in a control (healthy volunteer) group. Therefore, this investigation is restricted to the pSS subjects. In contrast there is a need to determine the kinetics and distribution of the ^{11}C-MET PET tracer in healthy volunteers and to define normal uptake of this tracer in the glands of interest, thus justifying the use of this imaging technique in the healthy volunteers. Similarly, it will be important to have control data from healthy volunteers when interpreting the DCE/DW MRI salivary gland data in the pSS subjects. Radiation exposure will be minimized by in-stream review of the variability of imaging parameters to determine the optimal sample size for each scan type.

Performing ^{18}F-FDG, ^{11}C-MET PET/CT scans, the salivary gland MRI scan as well as the minor salivary gland biopsy, laboratory biomarkers (including metabolomics and proteomics) and clinical assessments in the same pSS subject should allow assessment of associations between these endpoints. For example, in the same subject it should be possible to determine whether there are changes suggestive of salivary gland inflammation on ^{18}F-FDG-PET/CT or MRI, correlate this with the histology, and secondly to determine whether these inflammatory changes have an impact on function as determined by protein synthesis within the glands and salivary flow/symptoms. It will also be possible to understand whether there is a decrease in protein synthesis in the gland in the absence of inflammation (*eg*. inactive scarred disease). Looking at these potential associations between the imaging, histology and clinical assessments (*eg*. salivary flow) should help to determine whether they would be useful to characterize the disease in proof of mechanism studies in patients with pSS.

The study will also help to define whether there is inflammation in glandular structures or organs systemically, to correlate this with ESSDAI and subcomponents, and to assess whether gland function (protein synthesis) in these organs is impacted by any potential inflammation.

Published literature suggests there is a correlation between increased age and reduced salivary flow [Affoo, 2015], based on data from a meta-analysis of a large number of studies, and of a degree of potential relevance. Therefore, an attempt will be made to match the mean age of the healthy volunteers to the pSS subjects' where possible, whilst restricting the age range of healthy volunteers to ≥ 40 years of age.

4.5. Dose Justification

An investigational medicinal product (IMP) will not be administered to subjects enrolled in this study.

Radiaton Exposure

The total radiation exposure **for the pSS subjects** who are subjected to the studies with ^{18}F-FDG and ^{11}C-MET including its associated low-dose CT scans is expected to be **9.7mSv**, below 10mSv which falls within the Goup IIb, intermediate risk category as per the International Commission of Radiological Protection (ICRP) and generally considered ethically acceptable also for healthy volunteers *ie* 5.2mSv for the ^{18}F-FDG and associated CT, and 4.5mSv for the ^{11}C-MET components.

The healthy volunteers undergoing PET/CT will only receive ^{11}C-MET with its associated low-dose CT scans and hence be exposed to **4.5mSv**.

The average yearly radiation exposure from naturally occurring background radiation in the United Kingdom (UK) is 2.3mSv. Approval will also be obtained from the UK Administration of Radioactive substances Advisory Committee (ARSAC) prior to commencement of the study.

4.6. Benefit:Risk Assessment

The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Minor salivary gland biopsy (Group B only)	This procedure is associated with (a low) incidence of complications including discomfort, bleeding and haematoma formation.	**Subject selection:** • Subjects with bleeding disorders will be excluded from the study (exclusion # 4). • Subjects with an abnormal clotting screen or low platelet counts will be excluded from the study (exclusion #21). • Subjects who are unable to discontinue anti-coagulant medication to allow biopsy will be excluded(exclusion #16). **Subject management** • Local anaesthetic will be administered to reduce discomfort. • The biopsy will be performed by qualified physicians, surgeons or dentists with appropriate training and experience in the procedure
Subject exposed to ionizing radiation	**Radiation exposure from PET/CT scanning**: Radiation exposure from PET/CT scanning comes from two sources: the radionuclide injected for PET scanning, and the exposure to X-rays from the CT component. The estimated radiation doses for the whole study are 9.7mSv for pSS subjects and 4.5mSv for healthy volunteers. A typical diagnostic whole body CT scan would result in an exposure of around 10-15mSv.	**Study design:** 1. Low dose CT will be employed to minimize radiation exposure. 2. Subject age is restricted to ≥40 years for healthy volunteers and ≥30 years for pSS subjects to restrict radiation exposure for younger subjects (inclusion #1 and #4). 3. In stream data reviews will be performed to minimize the number of scans

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	An exposure of 9.7mSv approximates to 4 years of background radiation in the United Kingdom, and the additional risk of developing a fatal malignancy as a result of an exposure of 9.7mSv for the pSS subjects has been estimated as approximately 1 in 2100 for an adult in normal health. For healthy volunteers the total maximum effective dose of 4.5mSv is equivalent to approximately 2 times the average yearly exposure to background radiation and the additional risk of developing a fatal malignancy as a result of these exposures has been estimated at 1 in 4400 for an adult in normal health [ICRP, 2007]. To put this into context, in developed countries, the overall population risk of dying of cancer is 1 in 5 for females and 1 in 4 for males. Exposures of less than 10mSv are generally considered acceptable for research in healthy volunteers (*for discussion of potential foetal toxicity see separate section below).*	involving ionizing radiation that will be conducted
Potential radiation exposure to foetus of pregnant subject	**Ionizing radiation from CT scans and PET tracers** The potential risks of concern from foetal exposure to ionizing radiation are non-cancer adverse effects (*eg* miscarriage, malformation), and risks of childhood cancer. If for any reason a pregnant subject is	**Study design:** • Pregnant females are not eligible for the study (inclusion # 9). • Female subjects considering the study will be advised about the need to avoid pregnancy during the study until Follow up, and about the contraceptive and pregnancy testing requirements of the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	scanned, radiation exposure to the foetus from the whole study would be in the order of 10mGy or less for the pSS subjects, and lower for healthy volunteers. No non-cancer foetal adverse effects of radiation exposure (*eg* miscarriage, foetal malformation) have been detected below 50mGy exposure. For a foetus exposed in utero to 10mGy of radiation, the absolute risk of cancer at ages 0-15 years of age is about 1 excess cancer death per 1700 exposed (Annals of the IRCP, Volume 30, 1, 2000 (ICRP, 2000).	study before consent. • Females of reproductive potential will be required to use highly effective methods of contraception (as specified in the protocol) for 28 days prior to Visit 1 until Follow up. **Subject monitoring and management:** • Females of reproductive potential will undergo pregnancy testing to exclude pregnancy prior to scanning as described in inclusion #9. • **Withdrawal criteria:** In the event of a pregnancy in a female subject in the study, the subject will be withdrawn.
Subject exposed to gadolinium containing MRI contrast agents	The study uses DOTAREM (gadoterate meglumine) as an MRI contrast agent. **Non clinical data (source: gadoterate meglumine Summary of Product Characteristics (SPC)** The recommended clinical dose is 0.1mmol/kg (*ie* 0.2mL/kg). The administration of DOTAREM in rats and in dogs at daily doses up to 3mL/kg (*ie* 15 times the dose laid down in clinical conditions) and for 28 days cause no other effect than a reversible vacuolisation of the proximal tubular cells of the kidney.	**Subject selection:** • Subjects with impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/minute/1.73m^2) are excluded by the eligibility criteria (exclusion #20). • Subjects with a history of sensitivity to gadoterate meglumine containing contrast agents will be excluded from the study (exclusion #18). The site(s) will be responsible for following any additional safety guidelines for the specific gadoterate meglumine containing contrast agent used at the site and not scan

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Preclinical studies have demonstrated that DOTAREM is non-toxic for gestating females, non embryo-toxic and non teratogenic for the foetus. No prior peri- and post-natal toxicity and fertility studies have been carried out (source: SPC). **Clinical data:** Use of MRI contrast agents in subjects with severely impaired renal function Glomerular Filtration Rate (GFR) <30mL/minute has been associated with Nephrogenic Systemic Fibrosis (NSF)] (this is a class risk rather than specific for this particular agent). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed against the risks. Gadolinium (Gd) contrast agents can be associated with anaphylactoid or hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular respiratory or cutaneous manifestations, and ranging to severe reactions including shock. The risk of hypersensitivity reactions may be higher in case of previous history of reactions, bronchial asthma and history of allergic disorders. Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely	subjects if contra-indicated(exclusion #19). **Subject monitoring and management** • The MRI procedure will be conducted under the supervision of trained and qualified clinical staff who are trained to appropriately manage an allergic reaction. • MRI contrast at a dose less than or equal to 0.1mmoL/kg will be used. If it is necessary for technical reasons to repeat the MRI (no more than once), gadolinium contrast administration will not be repeated within a 24 hour period. *For pregnancy risk mitigations please see section above (potential radiation exposure to foetus of pregnant subject).*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	observed	
Subject exposed to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner	**Subject selection:** All participants will be screened according to local scanner criteria and trial inclusion/exclusion before entering the MRI room to ensure they are able to have the MRI conducted. Subjects with non-MR compatible metal implants or implantable electronic devices (*eg* pacemaker, defibrillator) will not be included in the study (exclusion #8).
Administration of PET tracers ^{18}F-FDG and ^{11}C-METhionine (including potential risks to a fetus of a pregnant subject)	**^{18}F-FDG PET Tracer:** Nonclinical data: Toxicological studies with a single intravenous (IV) injection of ^{18}F-FDG at 50-fold human dose in dogs and 1000-fold human dose in mice have not identified potential risks of clinical significance. **^{11}C-MET PET tracer** Methionine is an essential amino acid that is not synthesized *de novo* in humans, who must ingest methionine or methionine containing proteins. The daily adult requirement of methionine is 10mg/kg [Protein and amino acid requirements in human nutrition. Report of a joint Food and Agriculture Organization of the United Nations (FAO)/ World Health Organisation (WHO)/ United Nations University (UNU) expert consultation [WHO, 2007]. The dose	**Study design:** • The ^{11}C-MET will be produced according to Good Manufacturing Practice (GMP), and the specifications in the European Union (EU) Pharmacopoeia. • ^{18}F-FDG is purchased from a commercial producer, in accordance with product labelling. • The radiotracers will be administered at doses according to product labelling (where available) and the EU Pharmacopoeia. • Staff handling the tracers will have the necessary training and authorizations in their use. • For pregnancy risk mitigations please see section above (potential radiation exposure to foetus of pregnant subject).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	administered is several hundred fold less than the recommended daily intake of this essential amino acid. It is not anticipated that there will be any risks (reproductive or other) of the molecule itself (excluding ionizing radiation), although no foetal reproductive toxicity data is available	

4.6.2. Benefit Assessment

This study does not involve the use of an investigational medicine; therefore, participation will provide no therapeutic or direct medical benefit to participating individuals. However, it is anticipated that the data collected from this investigation will improve understanding of the relationship between structure, function and inflammation in pSS. Furthermore, subjects completing the study will potentially aid future improvement of the quality of care of pSS subjects by contributing to the development of improved imaging methods.

4.6.3. Overall Benefit: Risk Conclusion

Based upon the safety strategies and risk mitigations inherent to this protocol, GlaxoSmithKline (GSK) concludes the Benefit:Risk for a subject's participation in the GSK study 203818 is adequate and supports the study conduct.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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:

GROUP A: Healthy Volunteers

AGE
1. **Subjects for both PET/CT and MRI**: Aged >=40 years inclusive at the time of signing the informed consent. 2. **Subjects for MRI, without PET/CT**: Aged >=30 years inclusive at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
3. Healthy as defined by the investigator, or medically qualified designee, based on a medical evaluation including medical history, physical examination, and laboratory tests. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion/exclusion criteria may be included only if the investigator in consultation with the GSK Medical Monitor, if required, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

GROUP B: Primary Sjögren's Syndrome Patients

AGE
4. Age >=30 years, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
5. Diagnosis of primary Sjögren's Syndrome according to the American-European Consensus Group criteria [Vitali, 2002]. 6. Baseline unstimulated salivary flow >0.0mL/min or evidence of glandular reserve function (stimulated baseline salivary flow >0.05mL/min). 7. Systemically active disease, ESSDAI >=5 points.

All Subjects

WEIGHT
8. Body weight >=50 kg and body mass index (BMI) within the range 18.5 to 35 kg/m^2 (inclusive).

SEX
9. Male or Female, where one of the following conditions apply: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test) at screening, and a negative urine pregnancy test 3-8 days prior to Visit 1, on the day of Visit 1 (on each day of scanning), on Visit 2, is 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 use a male condom PLUS one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP), Section 12.3 (Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information) from at least 28 days prior to Visit 1, until after the completion of the follow-up visit. • The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
10. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF).

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 (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Diagnosis of secondary Sjögren's Syndrome. 2. Diagnosis of another systemic autoimmune disease, apart from pSS, including but not limited to, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis or systemic vasculitis. For Group B subjects, autoimmune conditions associated with pSS (for example autoimmune thyroiditis, primary biliary cirrhosis or coeliac disease), are not included in this exclusion, but should be described in the medical history taken baseline. If in doubt please consult the medical monitor. 3. Subjects with active life-threatening or organ-threatening effects of pSS meaning that they may not be able to complete the study visits according to the protocol (as determine by the investigator) (Group B). 4. History of coagulation or bleeding disorders which would increase the risk of minor salivary gland biopsy (for example but not limited to Haemophilia A or B, Von Willibrand's disease, platelet function disorders) (Group B). 5. History of malignancy within 5 years of screening that, in the view of the investigator, in consultation with the medical monitor if required, could confound the results of the ^{18}F-FDG PET/CT scan (including lymphoma associated with pSS). This does not include cervical carcinoma in situ or non-melanoma skin malignancy that has been treated with curative surgical treatment. 6. History of unresolved acute or chronic infection that, in the view of the investigator in consultation with the medial monitor, if required, could confound the results of the ^{18}F-FDG PET/CT. 7. Subject has diabetes mellitus requiring insulin therapy. 8. Contraindications to MRI scanning (as assessed by MRI safety questionnaire).

9. History of, or suffers from, claustrophobia or feel that they will be unable to lie still in the PET or MRI scanner for a period of up to 1 to 2 hours.
10. Where participation in the study would result in donation of blood or blood products in excess of 500mL within a 56 day period.
11. Previous inclusion in a research protocol involving nuclear medicine, PET or radiological investigations, or as a result of occupational exposure with a significant radiation burden (a significant radiation burden being defined as 10mSv in addition to natural background radiation, in the previous 3 years including the dose from this study). A clinical procedure where the subject received a direct benefit (eg diagnostic test) will not be included in the calculation of exposure.
12. Lack of adequate peripheral venous access for cannulation.
13. Current participation in a study with an investigational product, or recent participation within 5 half lives of discontinuation the drug, or within twice the duration of the biological effect of the drug, whichever is longer.

CONCOMITANT MEDICATIONS

14. Group A: healthy volunteers. Subject is unable to refrain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days prior to Visit 1 until completion of Visit 2, unless in the opinion of the investigator and Sponsor the medication will not interfere with the study.
15. Group B- pSS subjects taking immunomodulatory treatment at screening are excluded unless they have been on stable doses of these medicines for 6 weeks prior to Screening/Baseline and are expected to remain on stable doses of these medications until the Follow up visit. This would include drugs such as glucocorticoids, immunosuppressive agents (for example hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, and biologic therapies). Permitted medications are listed in Section 6.8. If in doubt please discuss with the Medical Monitor.
16. Group B: pSS subjects. Receiving treatment with anti-coagulant medications, including but not limited to warfarin, heparin, thrombin inhibitors, and Factor Xa inhibitors, and aspirin, unless the subjects is able to discontinue these medications one week prior to minor salivary gland biopsy, or according to local guidelines. The treatment may be restarted 3 days after the biopsy, or according to local guidelines.

RELEVANT HABITS

17. History of alcohol, prescription or non-prescription drug abuse which could interfere with participation in the trial according to the protocol, or in the opinion of the investigator impacts on the physical or mental wellbeing of the subject.

CONTRAINDICATIONS

18. History of allergy/hypersensitivity to study medications including local anaesthesia (Group B), radio-isotopes or gadolinium-containing contrast agents (all subjects).
19. Contraindications to gadolinium-containing contrast agents in accordance with product labelling and local guidelines.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
20. Estimated GFR [Modification of Diet in Renal Disease (MDRD) calculation] of less than 60mL/min/1.73m^2 at screening.
21. Platelet count below the laboratory normal range at screening, or prothrombin time above the laboratory normal range at screening (Group B).
22. Subject with a fasting blood sugar >11.1mmol/L at screening (defined as fasting for a minimum of 6 hours, excluding unflavoured water).

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 failure subjects meets the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (SAE) (see Section 7.3.1.4).

Subjects that are not enrolled into the study within the allotted screening window may be re-screened once. If re-screening is performed, subjects are assigned a different unique subject ID number for the re-screening, and all screening procedures must be repeated. See the SRM for specific details.

5.4. Withdrawal/Stopping Criteria

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.
- The subject becomes pregnant.
- The subject develops an allergic reaction to imaging contrast agents or any study administered treatments (radio-isotope, gadolinium, local anaesthesia), including anaphylaxis.
- The subject experiences a clinically significant severe AE or SAE that has a reasonable possibility of being related to study procedures.
- The study is discontinued by the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the site 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 the subject wishes to 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".

5.4.1. Liver Chemistry Stopping Criteria

There is no IMP in this study therefore there are no liver chemistry stopping or increased monitoring criteria.

5.4.1.1. Study Treatment Restart or Rechallenge

Not Applicable

5.4.2. QTc Stopping Criteria

There is no IMP in this study therefore there are no QTc stopping criteria for this study.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the Follow up.

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

6. STUDY TREATMENT

6.1. Investigational Product or other Study Treatment

There is no IMP in this study. Imaging agents are listed in Table 1.

Table 1 Study Treatments

	Study Treatment		
Product name: (Generic name and trade)	^{18}F-FDG (Group B only)	^{11}C-MET	Gadoterate meglumine (Dotarem)
[Formulation description:]	Refer to the summary of product characteristics (SmPC).	In accordance with EU Pharmacopoeia.	Refer to SmPC.
Dosage form:	Refer to SmPC.	Refer to study procedures manual (SRM)	Refer to SmPC.
Unit dose strength(s)/Dosage level(s):	200MBq.	500MBq.	Dose less than or equal to 0.1mmol/kg
Route of administration	For IV injection	For IV injection	For IV injection
Dosing instructions:	Refer to SmPC	Please refer to SRM	Please refer to SmPC
Physical description:	Refer to SmPC	Refer to SmPC	Refer to SmPC
Method for individualizing dosage:	None	None	Dose on mg/kg basis.

6.2. Blinding

This will be an open-label study.

6.3. Packaging and Labelling

^{18}F-FDG and DOTAREM will be purchased from commercial suppliers. ^{11}C-MET will be produced by Imanova, and the contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

Imaging agents will be prepared, handled and stored according to product labels, where available, and applicable regulatory requirements.

6.5. Treatment of Study Treatment Overdose

Imaging agent overdose will be managed according to product labels, where available, and local SOPs.

6.6. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because no medicinal products are being investigated in this study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

6.7. Lifestyle and/or Dietary Restrictions

- Subjects should refrain from alcohol in the 24 hours prior to all study visits.
- Subjects will be asked to eat a meal prior to the ^{11}C-MET scan in order to stimulate salivary gland function (details in SRM). Subjects should advise of any dietary restrictions so that a suitable meal can be organised (or if necessary can bring their own food by arrangement).
- Group B (pSS) patients will be asked to fast (with the exception of unflavoured water), for a minimum of 6 hours prior to the ^{18}F-FDG PET/CT scan.
- At the Screening/Baseline visit and Visit 2, the following restrictions apply, until after the collection of tears, saliva and plasma samples:
  - Subjects should fast for a minimum of 6 hours (with the exception of unflavoured water) until after sample collection.
  - Subjects will be required to withhold dosing with oral muscarinic agonists (such as pilocarpine and cevimiline) in the 12 hours prior to the Screening/Baseline visit and Visit 2.
  - For at least 2 hours prior to saliva collection, subjects should not brush their teeth or use oral hygiene products (including saliva substitutes or oral gels) or chewing gum, and not smoke.
  - Subjects should not use topical eye drops for 2 hours prior to tear collection until after tear collection.
  - Not apply eye makeup on the day of the visits, until after the tear collection.
  - Not wear contact lenses on the day of the visits, until after the tear collection.

6.7.1. Contraceptive Requirements

6.7.1.1. Female Subjects

Refer to eligibility criterion number 9 and Section 12.3 (Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information). The allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

6.7.1.2. Male subjects

There are no contraceptive requirements for male subjects in this study.

6.8. Concomitant Medications and Non-Drug Therapies

6.8.1. Permitted Drug Therapies (Group B: Primary Sjögren's Syndrome Subjects)

- Stable doses of potentially immunomodulatory treatments are permitted (stable from 6 weeks prior to screening until follow up). This includes potentially disease modifying drugs such as glucocorticoids, immunosuppressive agents (*eg* hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, and biologic therapies). The investigator should discuss drug therapies with the Medical Monitor if they have any safety concerns or are unsure about the potential impact on the scientific validity of the study data.
- Topical symptomatic therapies (such as [a] non-medicated ocular topical drops: saline or glucane; [b] non-pharmacologic oral topical agents: chewing gum, saliva substitutes) are permitted. Subjects will be required to withhold dosing with these agents in the 2 hours prior to collection of saliva and tear samples at Screening/Baseline visit and Visit 2.
- Oral muscarinic agonists (such as pilocarpine and cevimiline) are permitted. Subjects will be required to withhold dosing with these agents in the 12 hours prior to the Screening/Baseline visit and Visit 2.
- Anticholinergic agents, such as tricyclic antidepressants, buproprion, antihistamines, phenothiazines, antiparkinsonian drugs, anti-asthmatic medications, or gastrointestinal medications that cause xerostomia in more than 10% of patients are permitted provided that a subject is on a stable regimen for at least 4 weeks prior to Screening/Baseline visit until follow up has been completed.

6.8.2. Prohibited Medications and Non-Drug Therapies

Group A: Healthy Volunteers

- Healthy volunteers are to refrain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days prior to Visit 1 until after Visit 2, unless in the opinion of the investigator and Sponsor the medication will not interfere with the study.

Group B: Primary Sjögren's Syndrome Subjects

- Treatment with anti-coagulant medications, including but not limited to warfarin, heparin, thrombin inhibitors, and Factor Xa inhibitors, and aspirin, unless the subjects are able to discontinue these medications one week prior to minor salivary gland biopsy (Visit 2), or according to local guidelines. The treatment may be restarted 3 days after the biopsy, or according to local guidelines.

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 tables, is 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 Table 2 and Table 3

The change in timing or addition of time points for any planned study assessments must be documented in a Note to File approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Table 2 Time and Events Table – Screening and Baseline Assessments

Procedure	Screening/Baseline Visit	Baseline 2 (FRP only)
		Within 3-8 days prior to Visit 1
Informed consent	X	
Inclusion and exclusion criteria	X	
Demography	X	
Medical history including past and current medical conditions	X	
Full physical exam (including height and weight)	X	
MRI safety questionnaire	X	
Vital signs	X	
Concomitant medication review	X	
ESSDAI	X[1]	
ESSPRI	X[1]	
Oral dryness numerical rating	X[1]	
Ocular dryness numerical rating	X[1]	
Patient global assessment	X[1]	
Physician's global assessment	X[1]	
Basal salivary flow	X	
Stimulated salivary flow (including saliva collection)	X	
Schirmer's test (including tear collection)	X	
Plasma metabolomics/proteomics	X	
Haematology/clinical chemistry [see Table 4]	X	
Blood biomarkers for ESSDAI [see Table 4]	X[1]	

Procedure	Screening/Baseline Visit	Baseline 2 (FRP only)
		Within 3-8 days prior to Visit 1
Autoantibody screen (anti-Sjögren's-syndrome-related antigen A [Anti-SSa], anti Sjögren's syndrome type B [SSb])	X[1]	
FSH/oestradiol (post-menopausal women only)	X	
Serum pregnancy test (FRP)	X[2]	
Urine pregnancy test(FRP)		X[2]
Urinalysis	X[3]	

AE = adverse event; FSH = follicle stimulating hormone; MRI = magnetic resonance imaging; FRP = females of reproductive potential; .ESSDAI = European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index; ESSPRI =EULAR Sjögren's Syndrome Patient Reported Index

1. pSS subjects only
2. Females of reproductive potential only.
3. Urine to be sent for urine protein:creatinine ratio if ≥trace proteinuria by dipstick.

Table 3 Time and Events Table – Study Assessments

Procedure	Visit 1	Visit 2	Follow up
	Within 6 weeks after baseline	Within 3 weeks after Visit 1	Within 2 weeks after Visit 2
MRI safety questionnaire[5]	X		
Vital signs	X	X	
Concomitant medication review	X	X	
Basal salivary flow		X	
Stimulated salivary flow (including saliva collection)		X	
Schirmer's test (including tear collection)		X	
Plasma metabolomics/proteomics		X	
Urine pregnancy test (FRP)	X[1]	X[1]	
Multi-parametric MRI scan (including contrast)	X		
Meal prior to ^{11}C-MET PET/CT	X		
Intravenous injection of ^{11}C-MET PET tracer	X		
^{11}C-MET PET/CT scan (dynamic and static)	X		
Radio-PK (^{11}C-MET) sampling (dynamic scan)	X[2]		
Measure concentration of ^{11}C-MET tracer in blood	X[3]		
Blood glucose (bedside glucometer)	X[4]		
Injection of ^{18}F-FDG tracer	X[4]		
^{18}F-FDG PET/CT scan	X[4]		
Measure concentration of ^{18}F-FDG in blood	X[3,4]		
Salivary gland biopsy		X[4]	
AE review	X		

AE = adverse event; CT = computed Tomography; FDG = flurodeoxyglucose; FRP = females of reproductive potential; FSH = follicle stimulating hormone; MET = methionine; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics.

1. Females of reproductive potential only

2. Radio-PK sampling (5mL per sample) to be taken at 1, 2, 5, 10, 15, 20, 30 and 40 minutes after injection of ^{11}C-MET PET tracer (number and sampling times are subject to change dependent on emerging data, but no more than 100 mL overall will be taken).
3. To be taken within 5 minutes after the static PET/CT scan (exact time to be recorded).
4. pSS subjects only. If it is not possible to schedule the minor salivary gland biopsy within the 3 week window after Visit 1, this procedure may be performed up to 6 weeks after Visit 1, subject to prior agreement of the medical monitor.
5. The MRI safety questionnaire will not be databased.

7.2. Screening and Critical Baseline Assessments

7.2.1. For all subjects:

Information collected during the Screening/Baseline assessments described below represents key data that identifies and defines subject baseline status. This information is critical for the evaluation and comparison of subsequent imaging assessments. Additional assessments will be performed as detailed in the Time and Events tables, Table 2 and Table 3.

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 undergo screening assessments within 42 days prior to Visit 1. At screening 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 5.1 and Section 5.2. 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. 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 (where applicable, for Group A or Group B):

- Past or current conditions, including Sjögren's syndrome history.
- 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 (requiring inpatient treatment, 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).

Serum and urine pregnancy test: A test will be performed for women of child-bearing potential at Screening/Baseline. A urine pregnancy test will be repeated 3 to 8 days prior to Visit 1.

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.

Urinalysis: will be performed as related to the eligibility criteria listed in Section 5.1 and Section 5.2.

In addition, urinalysis will be performed in subjects included in Group B in order to calculate the ESSDAI score. If proteinuria is detected on dipstick (≥trace), quantification of the spot urine protein:creatinine ratio will be needed in the laboratory to calculate the ESSDAI score.

Haematology (including coagulation screen) **and blood chemistry (clinical safety laboratory assessments):** will be performed as related to the eligibility criteria listed in Section 5.1 and Section 5.2.

Female subjects:

FSH and oestradiol (females of non-reproductive potential only).

Serum hCG (at screening only) and urine hCG pregnancy test at other times as required (for females of reproductive potential).

Estimated Glomerular filtration rate (eGFR): will be calculated using the modification of diet in MDRD formula.

Unstimulated and stimulated salivary flow: Salivary flow rate will be assessed as an eligibility criterion for pSS subjects and a baseline procedure for all subjects. Subjects with 0.0mL/min unstimulated salivary flow rate may qualify for the study if their stimulated salivary flow is greater than 0.05mL/min. Details of the collection procedure will be further specified in the SRM.

Schirmer's test: This is an assessment of lacrimal gland function as a baseline procedure 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.

MRI safety questionnaire: in order to confirm eligibility for the MRI scan.

7.2.2. Additional baseline procedures for Group B subjects only (pSS Subjects)

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.

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 investigator. 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, 2014].

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 to 10 Numeric Rating Scale (NRS) for each symptom. The ESSPRI assessment tool will be detailed in the SRM.

Blood biomarkers (in order to confirm diagnosis and to calculate ESSDAI score: Quantification of serum autoantibodies (including anti-SS-A, SS-B), and immunological testing required for ESSDAI (including serum immunoglobulins [Total Immunoglobulin (Ig), IgG, IgA, IgM], protein electrophoresis, complement C3, C4, CH50 and C-reactive protein), bicarbonate and chloride. Cryoglobulin and urine electrophoresis testing is only needed if required for the calculation of ESSDAI score.

Oral and Ocular Dryness: will be reported by subjects on a numerical rating scale from 0 to 10. A description of the instrument anchors and technique for administering these scales will be described in the SRM.

Physician global assessment of disease activity: the Physician Global Assessment is a physician 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.

Patient global assessment of disease activity: 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.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events tables (Table 2 and Table 3). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE and SAE can be found in Section 12.2.

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

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (*eg* protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.
- AEs will be collected from Visit 1 until the follow up contact (see Section 7.3.1.4), at the time points specified in the Time and Events Tables (Table 2 and Table 3).
- Medical occurrences that begin prior to Visit 1 but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.2 (Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow up and Reporting of Adverse Events).
- 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 2.

7.3.1.2. 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?"

7.3.1.3. 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 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). Further information on follow up procedures is

given in Section 12.2 (Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow up and Reporting of Adverse Events).

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) 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. An IMP will not be administered to the subjects in this study. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/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 (*eg* summary or listing of SAEs) from GSK will file it with the Investigator Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

Details of all pregnancies in female subjects will be collected from Visit 1 and until follow up.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 12.3 (Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information).

7.3.3. Vital Signs

Single assessment of vital signs will be performed at the times indicated in the Time and Events Tables (Table 2 and Table 3). Vital signs will be measured in the semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.

7.3.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4 must be conducted in accordance with the SRM, and the Protocol Time and Events Schedule (Table 2 and Table 3). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation of samples are detailed in the SRM.

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 (*eg* SAE or AE) the results must be recorded in the CRF.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td><u>Full blood count indices</u></td><td><u>Red blood cell count Indices</u>:</td><td><u>White blood cell count with Differential</u>:</td></tr>
<tr><td>White blood count</td><td>Mean corpuscular volume (MCV)</td><td>Neutrophils</td></tr>
<tr><td>Platelet Count</td><td>Mean corpuscular haemoglobin</td><td>Lymphocytes</td></tr>
<tr><td>Haemoglobin</td><td>Mean corpuscular haemoglobin concentration</td><td>Monocytes</td></tr>
<tr><td>Haematocrit</td><td></td><td>Eosinophils</td></tr>
<tr><td><u>Coagulation screen</u></td><td></td><td>Basophils</td></tr>
<tr><td>Prothrombin time, Activated partial thromboplastin time</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry</td><td>
<table>
<tr><td>Urea</td><td>Potassium</td><td>Aspartate aminotransferase</td><td>Total bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine aminotransferase</td><td>Total Protein</td></tr>
<tr><td>Glucose (fasting for 6 h [excluding unflavoured water])</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
<tr><td>Creatine kinase</td><td>C-reactive protein</td><td>Chloride (pSS patients only)</td><td>Bicarbonate (pSS patients only)</td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal) and send urine for spot urinary protein:creatinine ratio</td></tr>
<tr><td>Other Screening Tests</td><td>• Follicle-stimulating hormone and oestradiol (as needed in females of reproductive potential only)
• Serum human chorionic gonadotropin (hCG) [at screening only] and urine hCG pregnancy test (as needed for females of reproductive potential)
• Group B only: anti-Sjögren's-syndrome-related antigen A (Anti-SSa),</td></tr>
</table>

Laboratory Assessments	Parameters
	anti-Sjögren's syndrome type B (SSb), total immunoglobulin (Ig), IgG, IgA, IgM, serum protein electrophoresis, complement C3, C4, CH50 • **Optional additional tests in Group B (if needed for calculation of ESSDAI):** cyroglobulins, urine electrophoresis, urinary protein creatinine ratio (if dipstick ≥trace protein). • Estimated glomerular filtration rate will be calculated using the modification of diet in renal disease (MDRD) formula.

NOTES :
European League Against Rheumatism (EULAR) primary Sjögren's syndrome disease activity [ESSDAI]

Safety laboratory tests are only conducted at screening in this study. Subjects with values that are considered clinically significantly abnormal will be assessed according to the inclusion/exclusion criteria. In the event of clinically significant laboratory values the investigator will advise the subject of appropriate clinical care.

7.4. Imaging Procedures

7.4.1. PET Imaging Procedure

Positron Emission Tomography scans will be acquired on a PET/CT scanner at the imaging centre. The details of the PET imaging procedure, image processing and analysis will be provided by the imaging centre in a PET Imaging Manual.

Subjects will be given a meal before the ^{11}C-MET tracer injection to stimulate salivary gland function.

Prior to the commencement of the PET scan a venous cannula will be inserted into the subjects arm for administration of ^{18}F-FDG or ^{11}C-MET. An additional venous cannula will also be inserted prior to the scan start from which blood samples will be collected at the time points described in the Time and Events tables Table 2 and Table 3. The subject will be positioned in the scanner and sufficient padding will be used to minimize movements during image acquisition. The subject will be monitored continuously by a qualified PET technician.

For ^{11}C-MET PET scanning, a low-dose CT attenuation scan centred on the salivary glands will be performed for subsequent attenuation and scatter correction of the PET data. Thereafter, the PET scan will commence with an intravenous bolus administration of ^{11}C-MET (500 MBq) and dynamic scanning of the salivary gland region for approximately 40 minutes. The static scan will follow (within approximately 5 minutes) with the whole body CT followed by the PET covering the head to hip with a duration of same range for approximately 20 to 30 minutes.

For ^{18}F-FDG PET scanning, scanning will start 60 minutes after intravenous bolus administration of 200 MBq of ^{18}F-FDG. Blood glucose (bedside glucometer) will be measured before injection of ^{18}F-FDG tracer. If the glucometer blood glucose is greater than 11.1mmol/l, the ^{18}F-FDG cannot be injected, and it will be necessary to reschedule

the scan. Advice for Investigators regarding diabetics on oral hypoglycaemic agents will be described in the SRM, and the scan will be scheduled in the morning for these subjects wherever possible. Firstly, a low-dose CT attenuation scan of the area to be scanned (head to hip) will be performed. Thereafter, the PET scan will commence with static scanning acquired for up to 30 to 40 minutes.

After the PET scans, a blood sample will be taken for measurement of radioactivity in blood and plasma (See Section 7.6).

After the scan the subjects will be allowed home at the discretion of clinical staff at the imaging facility.

7.4.2. MRI Imaging Procedure

As part of the study, eligible subjects will undergo multi-parametric MRI scanning, including administration of a gadolinium based contrast agent at the imaging centre to assess salivary gland inflammation, function and structure in pSS subjects and healthy volunteers. Additionally, the images may be used to identify and delineate the anatomical Regions of Interest (ROI) for individual PET images and to aid in image analysis.

On attendance at the MRI department, subjects will be placed in the scanner and will be prepared for intravenous contrast agent administration. The scanning protocol will include routine localizers, T1 measurement sequences, DCE-MRI acquisition, DW-MRI acquisition, and additional exploratory MRI endpoints, as detailed in the Imaging Acquisition Manual. The total scan time should not exceed 1 hour.

If a scanning failure occurs, if feasible a rescan is allowed within 7 days after the failed scan. There will be a minimum of 24 hours between scans where gadolinium contrast is used.

7.5. Image Analysis

All MRI and PET scans will be available at site, and will be reported at the site by a radiologist for clinical abnormalities per local standard procedures. If a significant clinical abnormality is identified that requires further investigation, the Investigator will be informed such that they can arrange appropriate investigations and medical care of the subject.

7.5.1. PET Image Analysis

Following reconstruction, scatter correction and attenuation correction, the PET data will be corrected for motion (if required) and if possible co-registered to each subject's structural MRI image. Anatomic regions of interest (ROIs) will be defined using a combination of each subject's PET/CT and MRI. Those ROIs will then be applied to the PET emission data to derive decay-corrected regional time-activity curves.

For the static head to hip ^{18}F-FDG and ^{11}C-MET scans, semi quantitative imaging outcome parameters (including standardized uptake value) will be generated from the decay corrected single time point activity measurement.

The primary structures to be included in the analysis include the different salivary glands, lymph nodes and pancreas whenever feasible with respect to size and signal intensity. Specific areas of increased FDG uptake in different areas of the body, for example including but not limited to the lungs will also be recorded and measured when possible.

Regions in normal structures like liver and blood pool in aorta may be included.

For the dynamic ^{11}C-MET scan, a radiometabolite-corrected plasma input function will be generated for each subject. The decay corrected time-activity curves will be analysed using a range of kinetic models including compartmental models and reference tissue models if a valid reference region is available in the field of view of the scan. The primary image outcome parameters will depend on the kinetics of the tracer in the region of interest and will be decided using quantitative criteria of model selection.

7.5.2. MRI Image Analysis

Reconstructed MR images for the various sequences will first be corrected for geometric distortion and subject motion, as needed and appropriate. Quality assurance procedures may be followed to assert image-characteristic consistency over the course of the study. These procedures may include checks on imaging metadata, as well as checks on the image data itself. Anatomical ROIs will be defined on structural MR imaging for salivary glands including both parotids glands and other major salivary glands if possible.

For the gadolinium enhanced perfusion sequence, a multiparametric model will be fitted for subject and for each point in the anatomical ROIs. This model will describe the wash-in of contrast medium following injection, the efflux of contrast medium from the capillaries to the extravascular space, and finally the wash-out of the medium from the tissue. The parametric maps obtained from the model, including maps for Ktrans, IRE and ME may then be used to calculate aggregate measurements per ROI.

Similarly, imaging data for the diffusion sequence will also be used to fit a multiparametric model. This model will describe the total diffusion of water as a composition of pure water diffusion and pseudo diffusion, *ie* the incoherent motion of water molecules due to capillary blood flow. Again, parametric maps, including maps for ADC, D and f may be used to compute aggregate measurements for each of the ROIs.

To investigate the complimentary relation between both imaging models, various combined models may be explored. This may include model based approaches such as alternative diffusion models that are informed by the tracer kinetic DCE model, but may also include data driven approaches such as higher level statistical analyses that are based on the parametric maps of both primary models.

These complimentary models are exploratory, but have the potential to generate outcome measures for future trials.

7.6. Pharmacokinetics

7.6.1. Blood sample collection and ^{11}C-Met radio PK analysis

Blood sample collection and analysis will be performed at Imanova Ltd.

Static ^{18}F-FDG and ^{11}C-MET acquisitions: At the end of each PET/CT scan, a single venous blood sample (3 mL) will be acquired for determination of whole blood and plasma radioactivity concentration.

Dynamic ^{11}C-MET acquisition: During the dynamic ^{11}C-MET PET acquisition, venous blood samples will be collected. Blood will be drawn in 5mL volumes at 1, 2, 5, 10, 15, 20, 30 and 40 minutes after injection of PET tracer. Sampling times and number of samples are subject to change, dependant on emerging data, but no more than 100 mL overall will be taken. The details of the time windows for the collection of these blood samples will be included in the SRM.

Tracer radioactivity concentration will be measured in plasma and whole blood, using a counter previously cross-calibrated with the scanner. In addition, metabolite analysis will be conducted on the plasma samples via High Performance Liquid Chromatography (HPLC). The timing of pharmacokinetics (PK) samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. In all instances, the actual time of each blood sample collection will be recorded. Blood samples collected during PET/CT imaging will be analysed immediately, and will not be stored. Processing and storage procedures are provided in the SRM.

7.7. Salivary gland biopsy (Group B)

A minor salivary gland biopsy will be performed on Visit 2 (pSS subjects only). The salivary gland biopsy surgical technique and sample handling will be described in the SRM and a training video will be made available with details of the procedure. Biopsy tissue will be shipped to a histopathology laboratory for processing and assessment. Histological assessments performed on salivary gland tissues will be conducted as described in Section 7.8.1.3.

7.8. Biomarker(s)/Pharmacodynamic Markers

7.8.1. Novel Biomarkers

7.8.1.1. Metabolomic Research

Biofluid (saliva, tears and plasma) metabolome studies may be performed by nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS, Liquid Chromatography [LC]-MS, Gas Chromatography [GC]-MS and/or Fourier Transform [FT]/MS) and/or equivalent methods. This may be done to compare the metabolome of pSS subjects with healthy volunteers, as well as to assess the variability in the metabolome and/or proteomic profile of individual subjects taken at 2 separate time points (Baseline and Visit 2). A comparison of the metabolomic and/or proteomic profile from different body fluids (saliva, tears and plasma), and their utility in distinguishing

pSS subjects from healthy volunteers may also be investigated. Associations between the metabolome data with proteomic data, clinical, serum biomarker, histological and imaging parameters may be studied.

7.8.1.2. Proteome Research

Biofluid (saliva, tears and plasma) proteome studies may be performed by 2-D gel separation, and/or peptide mass mapping, or an alternative equivalent procedure. These differentially expressed proteins may be identified by mass spectrometry or equivalent technology. Intra-subject variability may be assessed by comparing the proteomic profile of individuals at two different time points (Screening/Baseline and Visit 2). Comparisons may be made between the proteomic profiles of pSS subjects and healthy volunteers. Association of the observed proteomic parameters with clinical, imaging and immunological, serum biomarker, metabolome and histological parameters may be performed. Samples for longitudinal analysis will be collected and stored as described in the SRM and may be analysed at the end of the study.

The same samples may also be used to confirm findings by application of alternative technologies.

7.8.1.3. Salivary gland histological assessment

Histological assessments of salivary gland tissue will include a determination of lymphocyte infiltrate by Immune Histochemistry (IHC) (B and T cell subsets) and assessed through haematoxylin and eosin staining for foci scoring. The IHC assessment may include, (but not be limited to): B cell markers: CD20, IgG, IgM, IgA and CD38; T cell markers: CD3; markers of germinal centre formation: CD21 and markers of dividing cells: Ki67. Confocal microscopy or other specialist imaging techniques may be employed to image immunofluorescence stained sections.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined 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 Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.
- Case report forms (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to explore the use of ^{18}F-FDG PET/CT, ^{11}C-MET PET/CT, and multi-parametric MRI in pSS subjects and/or healthy volunteers. Due to the exploratory nature of this study, there are no formal hypotheses being tested.

For ^{11}C-MET PET/CT and multi-parametric MRI, summary statistics will be used to interpret each derived parameter. An exploratory comparison of pSS subjects vs healthy volunteers may performed for each ^{11}C-MET PET/CT and multi-parametric MRI derived quantitative parameter as data permits, to estimate difference (or ratio if log transformation is needed) with 95% confidence interval.

For ^{18}F-FDG PET/CT where only pSS subjects will be scanned, summary statistics will be used to present each derived parameter.

9.2. Sample Size Considerations

This is an exploratory study and therefore no formal sample size calculations have been conducted. Sample size is primarily driven by feasibility and knowledge of disease heterogeneity to sufficiently evaluate the primary and supportive secondary objectives of the study.

Group A: Healthy Volunteers:

Approximately 4 to 12 subjects will be recruited. After approximately 4 subjects have been scanned, the variability in the imaging parameters will be assessed, after which up to 8 additional subjects may be recruited as following: a maximum of an additional 4 for ^{11}C-MET PET/CT plus MRI (total maximum of 8 subjects for ^{11}C-MET PET/CT), with the option for 4 extra for MRI only (total maximum of approximately 12 subjects for MRI).

Group B: Primary Sjögren's Syndrome Subjects

Approximately 8 to 12 pSS subjects will be recruited. Due to anticipated greater variability amongst patients, the variability of the imaging parameters will be assessed after approximately 8 subjects have been recruited, and consequently up to an additional 4 subjects may be recruited.

Following a literature review the following information was obtained for the imaging modalities of interest in the parotid glands in different populations. This historical information can be used in the variability assessment as outlined above.

Imaging modality; Parameter	Healthy Volunteers Mean [SD]	Patients (not pSS) Mean [SD] n	Patients (pSS) Mean [SD] n	Reference
^{18}F-FDG PET; SUV_{max}	n/a	1.80 [0.53] n=25	n/a	Basu, 2008
^{18}F-FDG PET; SUV_{max}	n/a	2.00 [not stated]	2.75 [0.61] n=32	Cohen, 2013
^{18}F-FDG PET; SUV	n/a	1.90 [0.68] n=78	n/a	Nakamoto, 2005
^{11}C-MET PET; SUV_{max}	6.00 [1.5] n=11	n/a	n/a	Isohashi, 2013
DCE MRI, K_{trans}	0.20 [0.04] n=11	n/a	0.26 [0.05] n=21	Roberts, 2008
SD=Standard Deviation				

Using estimates of parameter (this can be any parameter, SUV_{mean}, SUV, K_{trans}) variability, the precision of these estimates calculated as half width of a 95% confidence interval for the mean and expressed as distance from mean to limits, for 4, 8 and 12 subjects has been calculated (Table 5).

Table 5 Estimated Precision for the Mean of an Imaging Parameter

SD	Precision of Mean		
	N=4	N=8	N=12
0.05	0.08	0.04	0.03
0.5	0.80	0.42	0.32
1	1.59	0.84	0.64
1.5	2.39	1.25	0.95

For example, based upon the estimate of variability of 1 and a sample size of 12, it is estimated that the lower and upper bounds of the 95% confidence interval for the means of the imaging parameter (e.g. SUV_{mean}, SUV, K_{trans}) will be within approximately 0.64 of the point estimate.

9.2.1. Sample Size Sensitivity

No sample size sensitivity has been performed.

9.2.2. Sample Size Re-estimation or Adjustment

The variability of healthy volunteers will be assessed for the ^{11}C-MET PET/CT and multi-parametric MRI imaging modalities after approximately 4 healthy volunteers have been scanned, and with the aid of precision estimates for the observed variability outlined in Table 5, a recommendation may be made to increase the total healthy volunteers sample size to up to 8 (for both PET/CT and MRI). In this event, a further review of the multi-parametric MRI results may be performed after 8 healthy volunteers and a

recommendation made to increase to a total of 12 for this imaging modality only. For feasibility reasons in the interests of limiting the exposure of healthy volunteers to radiation, a cap of 8 healthy volunteers is set for PET/CT.

Similarly the variability of pSS subjects will be assessed for the ^{11}C-MET PET/CT, ^{18}F-FDG PET/CT and multi-parametric MRI imaging modalities after approximately 8 pSS subjects have been scanned, and with the aid of precision estimates for the observed variability outlined in Table 5, a recommendation may be made to increase the total pSS subjects to 12.

For both groups, if sufficient data is collected for one or both PET/CT techniques, but not the other assessments (for example MRI), the additional subjects will only undergo the investigations needed (*eg* MRI and Visit 2 procedures without one or both PET/CT techniques), in order to minimize radiation exposure.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria
Safety	• Comprised of all subjects who receive/undergo any Visit 1 procedure.
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a radio-pharmacokinetic sample was obtained and analysed.

Additional analysis population(s) maybe defined in the Reporting and Analysis Plan (RAP).

9.3.2. Interim Analysis

No formal interim analysis will be performed, however a review of the imaging results will be performed for sample adjustment depending on the variability of the data as described in Section 9.2.2.

9.4. Key Elements of Analysis Plan

9.4.1. Primary analyses

Data for FDG PET/CT will be listed and summarized by quantitative parameter and Region of Interest (ROI). The data will be further explored graphically to examine:

- The parameter values across relevant ROI for each pSS subject
- The between-subject variability in parameter values by ROI

- Summary measures calculated across all relevant ROI (*eg*. maximum uptake, average uptake, total inflammatory volume, total number of lesions) and how these summary measures vary between patients.

- Asymmetry in parameter values between left and right parotid glands

Similar analyses may be performed for quantitative data from ^{11}C-MET PET/CT and multi-parametric MRI. For those imaging modalities, both HV and pSS are scanned, such that all displays will additionally denote group. An exploratory comparison of pSS vs HV may be performed for each quantitative parameter as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval. Further details are outlined in the reporting analysis plan (RAP).

9.4.2. Secondary Analyses

Descriptive statistics and/or graphical displays will be generated for all derived parameters from dynamic PET imaging and PK analyses. If data permits, statistical analyses of ^{11}C-MET PET radio-PK modelling indices with ^{11}C-MET static imaging matrices will be conducted to assess correlation.

9.4.3. Other/Exploratory Analyses

Details of the planned analyses for exploratory objectives to compare imaging parameters, explore their potential associations and the correlation of signals to clinical assessment measures and laboratory markers will be defined in the RAP.

Further details of proposed analyses will be specified 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 enrolment of subjects begins.

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

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 International Conference for Harmonisation (ICH) 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 favourable opinion/approval of the study protocol and amendments as applicable.

- Obtaining signed informed consent.
- Investigator reporting requirements (*eg* reporting of AEs/SAEs/protocol deviations to IRB/IEC).
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study.
- 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 CRF will serve as the source document.

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

- 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 multicentre 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 images in digital form will also be retained and may be used for future further analysis.

The records must be maintained to allow easy and timely retrieval, when needed (*eg* 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 (*eg* 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 Publically 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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Exploratory endpoints may be evaluated and reported outside the main Clinical Study Report.

11. REFERENCES

Affoo R, Foley N, Garrick R, Siqueria W and Martin R. Meta analysis of salivary flow rates in young and older adults.. Journal of the American Geriatrics Society. 2015: 63, p2142-2151.

Bakheet, S. M. and J. Powe . "Benign causes of 18-FDG uptake on whole body imaging." Semin Nucl Med 1998, 28(4): 352-358.

Basu, S., Houseni, M. and Alavi, A. Significance of incidental fluorodeoxyglucose uptake in the parotid glands and its impact on patient management. Nuclear Medicine Communications, 2008, 29(4), pp.367-373.

Buus, S., C. Grau, O. L. Munk, D. Bender, K. Jensen and S. Keiding. "^{11}C-MET PET, a novel method for measuring regional salivary gland function after radiotherapy of head and neck cancer." Radiother Oncol 2004, 73(3): 289-296.

Cohen, C., Mekinian, A., Uzunhan, Y., Fauchais, A., Dhote, R., Pop, G., Eder, V., Nunes, H., Brillet, P., Valeyre, D., Fain, O. and Soussan, M. 18F-fluorodeoxyglucose positron emission tomography/computer tomography as an objective tool for assessing disease activity in Sjögren's syndrome. Autoimmunity Reviews, 2013, 12(11), pp.1109-1114.

Deloar HM, Fujiwara T, Nakamura T, Itoh M, Imai D, Miyake M, Watanuki S. Estimation of internal absorbed dose of L-[methyl-^{11}C]methionine using whole-body positron emission tomography. Eur J Nucl Med. 1998 Jun;25(6):629-33. PMID

DOTAREM Summary of product characteristics (SPC) [http://www.mhra.gov.uk/spc-pil/?prodName=DOTAREM%20SOLUTION%20FOR%20INJECTION&subsName=GADOTERIC%20ACID&pageID=SecondLevel]

Fox, R. I. "Sjögren's syndrome." Lancet 2005, 366(9482): 321-331.

Glaudemans, A. W., R. H. Enting, M. A. Heesters, R. A. Dierckx, R. W. van Rheenen, A. M. Walenkamp and R. H. Slart. "Value of ^{11}C-MET PET in imaging brain tumours and metastases." Eur J Nucl Med Mol Imaging 2013, 40(4): 615-635.

Gomes Pde, S., G. Juodzbalys, M. H. Fernandes and Z. Guobis. "Diagnostic Approaches to Sjögren's syndrome: a Literature Review and Own Clinical Experience." J Oral Maxillofac Res 2012, 3(1): e3.

Harris, S. M., J. C. Davis, S. E. Snyder, E. R. Butch, A. L. Vavere, M. Kocak and B. L. Shulkin (2013). "Evaluation of the biodistribution of ^{11}C-MET in children and young adults." J Nucl Med 2013, 54(11): 1902-1908.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.].

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

Helmick, C. G., D. T. Felson, R. C. Lawrence, S. Gabriel, R. Hirsch, C. K. Kwoh, M. H. Liang, H. M. Kremers, M. D. Mayes, P. A. Merkel, S. R. Pillemer, J. D. Reveille, J. H. Stone and W. National Arthritis Data. "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I." Arthritis Rheum 2008, 58(1): 15-25.

Houweling, A. C., T. Schakel, C. A. van den Berg, M. E. Philippens, J. M. Roesink, C. H. Terhaard and C. P. Raaijmakers. "MRI to quantify early radiation-induced changes in the salivary glands." Radiother Oncol 2011, 100(3): 386-389.

ICRP. Pregnancy and Medical Radiation. ICRP Publication 2000, 84. Ann. ICRP 30 (1).

ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103, 2007. Ann. ICRP 37 (2-4).

Isohashi, K., Shimosegawa, E., Kato, H., Kanai, Y., Naka, S., Fujino, K., Watabe, H. and Hatazawa, J. Optimization of [^{11}C]-methionine PET study: appropriate scan timing and effect of plasma amino acid concentrations on the SUV. EJNMMI Research, 2013, 3(1), p.27.

Nakamoto, Y., Tatsumi, M., Hammoud, D., Cohade, C., Osman, M. and Wahl, R. (). Normal FDG Distribution Patterns in the Head and Neck: PET/CT Evaluation1. Radiology, 2005, 234(3), pp.879-885.

Roberts, C., Parker, G., Rose, C., Watson, Y., O'Connor, J., Stivaros, S., Jackson, A. and Rushton, V. Glandular Function in Sjögren Syndrome: Assessment with Dynamic Contrast-enhanced MR Imaging and Tracer Kinetic Modeling—Initial Experience 1. Radiology, 2008, 246(3), pp.845-853.

Seror R, Bootsma H, Saraux A, et al. Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis 2014; Dec 5. Pii: annrheumdis-2014-206008.

Su GY, Xu XQ, Wang YY, Hu H, Shen J, Hong XN, Shi HB, and Wu FO. Feasibility study of using intravoxel incoherent motion MRI to detect parotid gland abnormalities in early-stage Sjögren syndrome patients. J. Magn. Reson. Imaging, 2015. doi:10.1002/jmri.25096. PMID: 26583877

van der Aart J, Hallett WA, Rabiner EA, Passchier J, Comley. RA Radiation dose estimates for carbon-11-labelled PET tracers.. Nucl Med Biol. 2012 Feb;39(2):305-14. doi: 10.1016/j.nucmedbio.2011.08.005. Epub 2011 Oct 26. Review. PMID: 22033023

Vitali C., S. Bombardieri, R. Jonsson, H. M. Moutsopoulos, E. L. Alexander, S. E. Carsons, T. E. Daniels, P. C. Fox, R. I. Fox, S. S. Kassan, S. R. Pillemer, N. Talal, M. H. Weisman and S. European Study Group on Classification Criteria for Sjögren's .

"Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group." Ann Rheum Dis 2002, 61(6): 554-558.

World Health Organization. Report of a joint FAO/WHO/UNU expert consultation (WHO Technical Report Series 935). 2007, ISBN: 92 4 120935 6.

Ziakas, P. D., L. S. Poulou and L. Thanos. "Towards integrating positron emission tomography for work-up of patients with Sjogren's syndrome and associated lymphomas." Autoimmun Rev 2014, 13(3): 327-329.

12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ADC	Apparent Diffusion Coefficient
AE	Adverse Event
AECG	American European Consensus Group
ALT	Alanine Transaminase
Anti-SSa	Anti-Sjögren's-syndrome-related antigen A
ARSAC	Administration of Radioactive substances Advisory Committee
AST	Aspartate aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computed Tomography
CV%	Percentage Coefficient of Variation
D	Pure Diffusion Coefficient
DCE	Dynamic Contrast Enhanced
DW	Diffusion Weighted
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EU	European Union
EULAR	European League Against Rheumatism
f	Microvascular Volume Fraction
FAO	Food and Agriculture Organization of the United Nations
FDG	Fluorodeoxyglucose
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FT	Fourier Transform
GC	Gas chromatography
GCP	Good Clinical Practice
Gd	Gadolinium
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
HV	Healthy Volunteers
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immune Histochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRE	Initial Rate of Enhancement
IV	Intravenous
IVIM	Intravoxel Incoherent Motion
K_{trans}	Exchange Rate
M	Meter
MedDRA	Medical Dictionary for Regulatory Activities
ME	Maximal Signal Intensity Enhancement
MET	Methionine
MRI	Magnetic Resonance Imaging
MS	Mass Spectroscopy
mSv	Millisievert
NRS	Numeric Rating Scale
PET	Positron Emission Tomography
PK	Pharmacokinetic
pSS	Primary Sjögren's Syndrome
RAP	Reporting Analysis Plan
ROI	Region of Interest
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SPC	Summary of product characteristics
SRM	Study Reference Manual
SSb	anti Sjögren's syndrome type B
TIV	Total Inflammatory Volume
UK	United Kingdom
ULN	Upper Limit of Normal
UNU	United Nations University
WHO	World Health Organisation

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Dotarem

12.2. Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow up and Reporting of Adverse Events

12.2.1. 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms (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. • 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. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> 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.

12.2.2. 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 fulfils 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.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

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

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- Alanine Transaminase (ALT) ≥ 3x Upper Limit of Normal (ULN) and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and International Normalised Ratio (INR)** >1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** 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.

12.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure

- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.2.4. 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 Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire 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.

12.2.5. 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.

12.2.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• 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 the SAE coordinator. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • 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 the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined oestrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. 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 [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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.

12.3.2. Collection of Pregnancy Information

Female Subjects Enrolled on the Study

- 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 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.
- Any termination of pregnancy will be reported, regardless of foetal 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. 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.

12.4. Appendix 4: Protocol Amendment Changes

Protocol Amendment 1 (24-MAY-2017) from the original protocol (13-Jun-2016)

Where the Amendment Applies

This amendment applies to all subjects who will participate in this study in all countries.

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

There are updates to some T&E windows (pregnancy tests, V1 for FRP and minor salivary gland biopsy) and blood tests as per file notes issued during study. Typographical error in Section 9.2 changed from "within approximately 0.62 of the point estimate" to "within approximately 0.64 of the point estimate". There are also minor formatting changes.

Section 4.1 Overall Design

Rationale for change

Pregnancy test window has been increased to allow additional flexibility around when the subjects need to attend the clinic.

There is no need for FRP to wait for 28-42 days after screening for Visit 1, as long as they fulfil the requirements in eligibility criterion #9 for 28 days prior to Visit 1 as listed.

In line with clinical practice, a physical visit is no longer considered necessary for follow up for pSS subjects. Flexibility to allow follow up to be conducted by telephone if deemed appropriate by the Investigator has been incorporated.

These changes have been updated throughout the protocol.

Revised Text

Third paragraph

If Females of Reproductive Potential (FRP) are included they must have a negative pregnancy test as determined by serum human chorionic gonadotropin (hCG) test at screening, and a negative urine pregnancy test **3-8** ~~4-7~~ days prior to Visit 1, and on Visit 1 ~~(which will occur 28-42 days after screening)~~. If Visit 1 is split over more than 1 day there must be a negative urine pregnancy test on each day, prior to scanning.

Fourth Paragraph

The follow up may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) **may have their Follow up visit conducted in person, or by telephone if the Investigator considers it clinically appropriate** ~~will return to the clinical unit for Follow up to allow for the examination of the salivary gland biopsy site~~.

Section 4.2 Treatment Arms and Duration, Visits

Rationale for change

Due to logistical difficulties experienced in scheduling the salivary gland biopsy within 3 weeks of visit 1, and the fact that the study team do not consider that a short delay would affect the scientific integrity of the study, additional flexibility around timing of the biopsy has been incorporated.

These changes have been updated throughout the protocol.

Revised Text

Third paragraph

In addition, a minor salivary gland biopsy will be performed on the pSS subjects (Group B). **If it is not possible, for logistical or other reasons to schedule the minor salivary gland biopsy within 3 weeks of Visit 1, then this part of Visit 2 may be performed up to 6 weeks after Visit 1, with the prior agreement of the medical monitor.**

Fourth paragraph

Visit 1 and Visit 2 may be split over more than one day. The total duration of participation in the study will be a maximum of 11 weeks **(14 only if it becomes necessary to delay the minor salivary gland biopsy)**, although the visits should be completed sooner if feasible.

Section 4.2 Treatment Arms and Duration, Follow up

Second paragraph

The total duration of the study will be up to 11 weeks **(14 only if it becomes necessary to delay the minor salivary gland biopsy)**, although ideally the study should be completed as soon as practicable within the time windows.

Section 4.6. Benefit: Risk Assessment

Section 4.6.1 Risk Assessment

Rationale for change

Typographical error corrected.

Revised Text

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential radiation exposure to foetus of pregnant subject	<u>Ionizing radiation from CT scans and PET tracers</u> The potential risks of concern from foetal exposure to ionizing radiation are non-cancer adverse effects (*eg* miscarriage, malformation), and risks of childhood cancer. If for any reason a pregnant subject is scanned, radiation exposure to the foetus from the whole study would be in the order of 10mGy or less for the pSS subjects, and lower for healthy volunteers. No non-cancer foetal adverse effects of radiation exposure (*eg* miscarriage, foetal malformation) have been detected below 50mGy exposure. For a foetus exposed in utero to 10mGy of radiation, the absolute risk of cancer at ages 0-15 years of age is about 1 excess cancer death per 1700 exposed (Annals of the IRCP, Volume 30, 1, 2000 (ICRP, 2000).	<u>Study design:</u> • Pregnant females are not eligible for the study (inclusion # 9). • Female subjects considering the study will be advised about the need to avoid pregnancy during the study until Follow up, and about the contraceptive and pregnancy testing requirements of the study before consent. • Females of reproductive potential will be required to use highly effective methods of contraception (as specified in the protocol) for **28** ~~30~~ days prior to Visit 1 until Follow up. Subject monitoring and management: • Females of reproductive potential will undergo pregnancy testing to exclude pregnancy prior to scanning as described in inclusion #9. • Withdrawal criteria: In the event of a pregnancy in a female

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		subject in the study, the subject will be withdrawn.

Section 7.3. Safety

Rationale for change

No central laboratory manual is used in this study, details are given in the SRM.

The listing of the additional blood biomarkers required, or potentially required for pSS subjects (Group B) to calculate the ESSDAI score was incomplete in the original approved protocol.

Thrombin Time and Direct Bilirubin tests are not part of the standard coagulation screen or liver screen, respectively, but are used to further investigate abnormalities. For the purposes of this protocol they are unnecessary and have been removed from Table 4.

These changes have been updated throughout the protocol.

Revised Text

Section 7.3.4 Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4 must be conducted in accordance with the ~~Laboratory Manual~~ **SRM**, and the Protocol Time and Events Schedule (Table 2 and Table 3). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation of samples are detailed in the SRM.

Table 4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Haematology	*Full blood count indices*	*Red blood cell count Indices*:	*White blood cell count with Differential:*
	White blood count	Mean corpuscular volume (MCV)	Neutrophils
	Platelet Count	Mean corpuscular haemoglobin	Lymphocytes
	Haemoglobin	Mean corpuscular haemoglobin concentration	Monocytes
	Haematocrit		Eosinophils
	Coagulation screen		Basophils

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td></td><td>
<table>
<tr><td>Prothrombin time, Activated partial thromboplastin time ~~Thrombin time~~</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry</td><td>
<table>
<tr><td>Urea</td><td>Potassium</td><td>Aspartate aminotransferase</td><td>Total ~~and direct~~ bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine aminotransferase</td><td>Total Protein</td></tr>
<tr><td>Glucose (fasting for 6 h [excluding unflavoured water])</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
<tr><td>Creatine kinase</td><td>C-reactive protein</td><td>Chloride (pSS patients only)</td><td>Bicarbonate (pSS patients only)</td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal) and send urine for spot urinary protein:creatinine ratio</td></tr>
<tr><td>Other Screening Tests</td><td>• Follicle-stimulating hormone and oestradiol (as needed in females of reproductive potential only)
• Serum human chorionic gonadotropin (hCG) [at screening only] and urine hCG pregnancy test (as needed for females of reproductive potential)
• Group B only: anti-Sjögren’s-syndrome-related antigen A (Anti-SSa), anti-Sjögren's syndrome type B (SSb), total immunoglobulin (Ig), IgG, IgA, IgM, serum protein electrophoresis, complement C3, C4, CH50
• Optional additional tests in Group B (if needed for calculation of ESSDAI): cyroglobulins, urine electrophoresis, urinary protein creatinine ratio (if dipstick ≥trace protein).
• Estimated glomerular filtration rate will be calculated using the modification of diet in renal disease (MDRD) formula.</td></tr>
<tr><td colspan="2">NOTES :
European League Against Rheumatism (EULAR) primary Sjögren's syndrome disease activity [ESSDAI]</td></tr>
</table>

Section 9.2. Sample Size Considerations

Rationale for change

Typographical error corrected.

Revised Text

Table 5 Estimated Precision for the Mean of an Imaging Parameter

SD	Precision of Mean		
	N=4	N=8	N=12
0.05	0.08	0.04	0.03
0.5	0.80	0.42	0.32
1	1.59	0.84	0.64
1.5	2.39	1.25	0.95

For example, based upon the estimate of variability of 1 and a sample size of 12, it is estimated that the lower and upper bounds of the 95% confidence interval for the means of the imaging parameter (e.g. SUV_{mean}, SUV, K_{trans}) will be within approximately **0.64** ~~0.62~~ of the point estimate.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A Pilot Study to Evaluate Molecular Imaging Methods in Primary Sjögren's Syndrome

Compound Number: None

Development Phase Not applicable

Effective Date: 13-JUN-2016

Author(s): PPD

SPONSOR SIGNATORY:

PPD

13th June 2016

Caroline Savage
VP & Head Experimental Medicine Unit
Immunoinflammation Therapy Area

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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	Dr PPD PPD	Tel: PPD Mobile: PPD PPD	Mobile: PPD	PPD	GSK Medicines Research Centre, Gunnels Wood, Stevenage, Hertfordshire, SG1 2NY, UK
Secondary Medical Monitor	Dr PPD PPD	Tel: PPD PPD	Mobile: PPD PPD		
SAE contact information	[Medical monitor as above]				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

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): NA

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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 Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 203818

Rationale

This is a pilot imaging study designed to assess whether molecular imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), ^{11}C-Methionine (MET) PET/CT and salivary gland magnetic resonance imaging (MRI) have the potential to characterize and quantify disease manifestations in primary Sjögren's syndrome (pSS) subjects. This will be achieved by assessing the associations and consistency between the imaging techniques studied, clinical assessments (salivary and tear flow and clinical scores), laboratory biomarkers and histological findings on minor salivary gland biopsy. It is hoped that the methodologies may help with the selection of subjects, and/or assessments of treatment response in future clinical studies. For example, subjects with on-going inflammation and a degree of gland function might be more suitable for anti-inflammatory therapies.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the use of ^{18}F-FDG PET/CT in assessing increased glucose uptake as a biomarker of inflammation in pSS subjects.	• Semi-quantitative parameters of uptake in selected body areas, including salivary glands for ^{18}F-FDG: – Standardised uptake value (SUV) – Tissue-to-reference ratio – Total inflammatory volume (TIV) where anatomically relevant.
• To investigate the use of ^{11}C-Methionine (MET) PET/CT in assessing salivary glandular function in pSS subjects and healthy volunteers.	• Semi-quantitative parameters of uptake in selected areas, including salivary glands for ^{11}C-MET: – SUV – Tissue-to-reference ratio – TIV where anatomically relevant.
• To investigate the use of multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including: exchange rate (K_{trans}), apparent diffusion coefficient (ADC), pure diffusion coefficient (D) and microvascular volume fraction (f) as data permits.

Secondary	
• To characterize the pharmacokinetics of ^{11}C-MET PET tracer *in vivo* to allow static imaging parameters to be verified.	• Generation of quantitative outcome parameters (rate of ^{11}C-MET accumulation, as data permits) using a full quantitative analysis of dynamic PET scans. • Comparison of static and dynamic imaging metrics in ^{11}C-MET.
Exploratory	
• To explore the use of novel multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including: initial rate of enhancement (IRE), maximal signal intensity enhancement (ME), lipid content, T1 relaxation, and volume, as data permits.
• To explore the associations of the salivary gland imaging parameters with clinical and histological parameters of salivary glands.	• Association between ^{18}F-FDG PET/CT (pSS subjects only), ^{11}C-MET PET/CT and MRI parameters (healthy volunteers and pSS subjects) in the region of the salivary glands with each other and with clinical measures including: – Basal and stimulated salivary flow – Histological scores from minor salivary gland biopsies including but not limited to lymphocyte count and focus score (pSS subjects) – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) – European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), in particular subcomponents relevant to salivary gland function (pSS subjects).
• To explore the extent of non-salivary	• Semi-quantitative parameters in

gland (systemic) abnormalities detected on ^{18}F-FDG PET/CT and ^{11}C-MET PET/CT, and the association of these abnormalities with clinical scores/relevant sub-scores and laboratory biomarkers in pSS subjects.	selected areas systemically for ^{18}F-FDG and ^{11}C-MET (including but not limited to lymph nodes, thyroid, lacrimal glands, lungs and pancreas) and the associations of these parameters with: – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) – Lacrimal gland function as measured by Schirmer's test – ESSDAI and ESSPRI and organ-specific subcomponents relating to the area imaged, where available.
• To compare the metabolomic profiles of pSS subjects and healthy volunteers, to assess the intra-individual variability of the metabolome over time, and the ability of samples from different bodily sites to discriminate pSS subjects from healthy volunteers.	• Compare the metabolome/proteome of pSS subjects with healthy volunteers. • Assess the variability in the metabolome and/or proteomic profile of individual subjects taken at 2 separate time points (Baseline and Visit 2). • Compare the metabolome and/or proteomic profile from different body fluids/sites, and their utility in distinguishing pSS subjects from healthy volunteers. • Samples collected will be saliva, tears and plasma.

Overall Design

Healthy volunteers will be enrolled in Group A and pSS subjects will be enrolled in Group B.

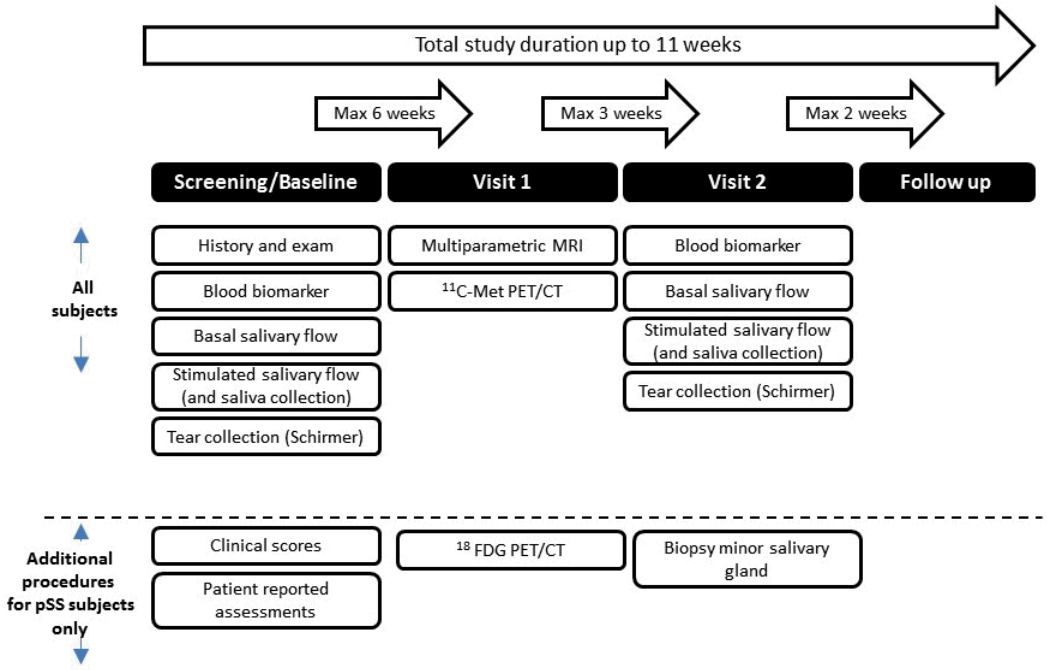
The subjects will be required to attend the clinical unit for a Screening/Baseline visit, an imaging visit (Visit 1) a sample collection visit (Visit 2) and a Follow up. The pSS subjects will have a minor salivary gland biopsy at Visit 2. Females of reproductive potential (FRP) will be required to have a negative pregnancy test as determined by serum hCG test at screening and will be required to have a negative urine pregnancy test 4-7 days prior to Visit 1, and on Visit 1 (which will occur 28-42 days after screening). If Visit 1 is split over more than 1 day there must be a negative urine pregnancy test on each day, prior to scanning.

All procedures will be performed as outpatient visits.

No investigational medicinal product (IMP) will be administered to subjects enrolled in this study.

Treatment Arms and Duration

Subject Participation Flow



Both groups will undergo a Screening/Baseline visit where they will have measurement of basal and stimulated, salivary flow rate (including saliva collection), Schirmer's test and blood samples for biomarkers. The pSS subjects will also have additional clinical scores and patient reported assessments.

Subjects who have completed the screening/baseline will return for an imaging visit (Visit 1). The imaging visit should occur within 6 weeks (42 days) after the screening visit (28-42 days after screening for FRP). The following imaging procedures will be performed:

- Group A (healthy volunteers) will undergo an MRI of the salivary glands and ^{11}C-MET PET/CT (dynamic scan of the salivary glands followed by head to hip static scan).

- Group B (pSS subjects) will undergo an MRI of the salivary glands, ^{11}C-MET PET/CT (as for Group A) and ^{18}F-FDG PET/CT (static scan head to hip).

Visit 2 will occur within 3 weeks after Visit 1. Visit 2 will involve measurement of basal and stimulated (chewing paraffin) salivary flow rate (including saliva collection), Schirmer's test (including tear collection), blood samples for biomarkers (metabolomics/proteomics). In addition a minor salivary gland biopsy will be performed on the pSS subjects (Group B).

There will be a Follow up visit within 2 weeks of Visit 2. This may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) will return to the clinical unit to allow the assessment of the salivary gland biopsy site. Adverse events (AE) will be reviewed at this visit for all of the subjects (Group A and Group B).

Visit 1 and Visit 2 may be split over more than one day.

The total duration of participation in the study will be a maximum of 11 weeks, although the visits should be completed sooner if feasible.

Type and Number of Subjects

Between approximately 4 to 12 healthy volunteers and between approximately 8 to 12 pSS subjects will be recruited into the study. As there is very little data about the variability of the imaging parameters, in-stream review of the variability will be conducted in order to determine the number of subjects that are required for PET/CT and/or MRI. In order to minimize radiation exposure to healthy volunteers, a maximum of 8 healthy volunteer subjects will undergo the ^{11}C MET PET/CT scan component.

As pSS affects females in about 90% of cases, and in order to reduce variability, initially only female healthy volunteer subjects will be recruited. If in the course of the study male pSS subjects are recruited, male healthy volunteers may be recruited at the discretion of the Sponsor. The ages of the healthy volunteers will be matched approximately to the ages of the pSS subjects as far as is practically possible, and within the age restrictions of the protocol.

Healthy volunteers and pSS subjects will be recruited simultaneously. However, there may be some staggering in the recruitment of subjects to allow approximate age and sex matching.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor.

Analysis

This is an exploratory study and therefore no formal sample size calculations have been conducted. Sample size is primarily driven by feasibility and knowledge of disease heterogeneity to sufficiently evaluate the primary and supportive secondary objectives of the study.

Descriptive statistics and graphical displays if appropriate will be presented for all ^{18}F-FDG PET/CT derived parameters across the regions of interest (ROI) for all pSS subjects and for all ^{11}C-MET PET/CT and multi-parametric MRI derived parameters across the ROI for all healthy volunteers and pSS subjects. An exploratory comparison of pSS subjects vs healthy volunteers may be performed for each ^{11}C-MET PET/CT and multi-parametric MRI derived quantitative parameter as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval. Descriptive statistics and graphical displays if appropriate will also be presented for all derived parameters from dynamic PET imaging and pharmacokinetic (PK) analyses. If data permits, statistical analyses and/or graphical presentation of radio-PK modelling indices with ^{11}C-MET static imaging matrices will be conducted to assess correlation.

2. INTRODUCTION

2.1. Study Rationale

This pilot study is designed to assess the potential value of imaging methods in pSS subjects. The selected imaging methods will include:

- Positron Emission Tomography (PET) / Computed Tomography (CT) with ^{11}C-Methionine (MET) imaging to characterize protein synthesis within the salivary and other glands as a potential marker of gland function;
- Multi-parametric Magnetic Resonance imaging (MRI) of the salivary glands to assess gland function, structure and potential biomarkers of inflammation; and
- PET/CT with ^{18}F-Fluorodeoxyglucose (FDG) as a marker of inflammation to assess disease extent in the salivary glands and systemically.

The aim of the study is to determine whether the imaging methodologies under investigation have the potential to characterize and quantify disease manifestations in Primary Sjögren's Syndrome (pSS) subjects. This will be achieved by assessing the associations between the imaging techniques studied, clinical assessments (salivary and tear flow and clinical scores), biomarkers (including metabolomics/proteomics) and histological findings on minor salivary gland biopsy. It is hoped that the methodologies may help in subject selection and/or assessment of treatment response in future clinical studies. For example subjects with on-going inflammation, and a degree of gland function might be more suitable for anti-inflammatory therapies.

2.2. Brief Background

Primary Sjögren's Syndrome (pSS) is a chronic systemic disease with a female over male preponderance of 9:1 [Vitali, 2002, Helmick, 2008] that primarily involves the salivary (xerostomia) and lacrimal (keratoconjunctivitis sicca) glands caused by inflammation [Fox, 2005 and Gomes Pde, 2012]. However, any organ or mucosal surface may be involved, with the risk of lymphoma development remaining the most serious complication [Ziakas, 2014].

There is a need to develop methods that can reduce both the time to diagnosis and assess the effect of current and new therapies in these patients in a more quantitative manner, in particular for assessing the heterogeneous nature of the disease, and selecting patients most likely to respond to therapies (*ie* those with active disease and a degree of gland function). Molecular imaging methods have the potential to provide 3D high resolution, sensitive and quantitative measures of disease manifestations, combined with whole body assessment for the PET methods. This makes them an attractive tool to consider for assessing disease status at entry to clinical studies, and potentially for monitoring treatment effects.

The methods under study are ^{18}F-FDG PET/CT as a measure of inflammation, ^{11}C-MET PET/CT as a measure of protein synthesis within the glands, and multi-parametric MRI to assess both structural and functional changes in salivary glands in pSS. Ultrasonography

has been used as a diagnostic tool in pSS, but its role in monitoring treatment effects in multicentre studies is more challenging and less clear.

Published literature around use of ^{18}F-FDG, ^{11}C-MET PET and multi-parametric MRI in pSS is limited as the methods are more commonly used in other indications: ^{18}F-FDG uptake is a marker for increased glucose uptake, which is closely correlated to certain types of metabolism such as that of malignant cells but it is also a feature of inflammation with inflammatory foci exhibiting high ^{18}F-FDG uptake [Bakheet, 1998]. In pSS, the relation of ^{18}F-FDG uptake to inflammation needs to be further explored but a recent report by Ziakas [Ziakas, 2014] showing a strong correlation between inflammation and FDG uptake in Sjögren's patients treated for salivary lymphomas is encouraging [Ziakas, 2014]. In addition, Cohen *et al*. [Cohen, 2013] reviewed the PET data from 32 Sjögren's patients that underwent ^{18}F-FDG PET and showed that ^{18}F-FDG uptake was increased in 75% of patients with 60% displaying increased uptake in lymph nodes, 50% in the parotid glands, 28% in the submandibular glands, 28% in the lung and 6% in the thyroid.

Salivary gland disease is a hallmark for pSS and PET with ^{11}C-MET can potentially assess function with a superior sensitivity and anatomical resolution than the gold standard contrast sialography or salivary gland scintigraphy with ^{99m}Tc-sodium pertechnectate. ^{11}C-MET, a labelled essential amino acid, is most popular for PET imaging of brain tumours; events such as cellular proliferation are associated with increased protein synthesis and hence avid uptake of these precursors [Glaudemans, 2013]. Furthermore, ^{11}C-MET has been used for measuring liver protein synthesis and assessing excretory pancreas function [Harris, 2013]. Dynamic ^{11}C-MET has been used as a quantitative measure of regional gland function in the major salivary glands in head-and-neck cancer patients that underwent loss of salivary gland function as a result of radiotherapy [Buus, 2004]. This study aims to determine whether there is a disturbance in protein synthesis in salivary glands that correlates to disease activity, although the relationship between inflammation and gland function (protein synthesis) in pSS is as yet unclear. In addition, the ability of PET to image the whole body will also allow recording of function in other glands such as the pancreas.

Magnetic resonance imaging (MRI) offers a superior soft tissue contrast and high resolution to assess anatomical organ changes (using T1 or T2 weighted) *in vivo*, also non-invasively. Furthermore, functional imaging techniques are also available using MRI: Dynamic Contrast Enhanced (DCE)-MRI provides information about the microvasculature of tissues. Since the salivary glands are highly perfused, this technique may be adequate for the evaluation of damage to the vessels in the salivary glands [Houweling, 2011]. Diffusion Weighted (DW)-MRI maps the diffusion process of molecules, mainly water, and yields qualitative and quantitative information reflecting tissue cellularity and cell membrane integrity. The intravoxel incoherent motion (IVIM) model of diffusion may be sensitive to early microstructural changes to the parotid gland in pSS patients [Su, 2015]. It thereby complements the morphological information obtained by conventional MRI. Roberts and colleagues [Roberts, 2008] compared the parotid gland microvascular characteristics in 21 patients with Sjögren's syndrome with those in 11 healthy volunteers. They demonstrated significant differences in DCE parameters with patients also displaying greater gland heterogeneity [Roberts, 2008].

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To investigate the use of ^{18}F-FDG PET/CT in assessing increased glucose uptake as a biomarker of inflammation in pSS subjects.	• Semi-quantitative parameters of uptake in selected body areas, including salivary glands for ^{18}F-FDG in selected areas: – Standardised Uptake Value (SUV) – Tissue-to-reference ratio – Total Inflammatory Volume (TIV) where anatomically relevant.
• To investigate the use of ^{11}C- MET PET/CT in assessing salivary glandular function in pSS subjects and healthy volunteers.	• Semi-quantitative parameters of uptake in selected areas, including salivary glands for ^{11}C-MET : – SUV – Tissue-to-reference ratio – TIV where anatomically relevant.
• To investigate the use of multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including: Exchange rate (K_{trans}), Apparent Diffusion Coefficient (ADC), pure diffusion coefficient (D) and microvascular volume fraction (f) as data permits.
Secondary	
• To characterize the pharmacokinetics of ^{11}C-MET PET tracer *in vivo* to allow static imaging parameters to be verified.	• Generation of quantitative outcome parameters (rate of ^{11}C-MET accumulation, as data permits) using a full quantitative analysis of dynamic PET scans. • Comparison of static and dynamic imaging metrics in ^{11}C-MET.
Exploratory	
• To explore the use of novel multi parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy	• Quantitative parameters of uptake derived from multi-parametric MRI in the salivary glands including, Initial Rate of Enhancement (IRE),

volunteers.	maximal signal intensity enhancement (ME), lipid content, T1 relaxation and volume, as data permits.
• To explore the associations of the salivary gland imaging parameters with clinical and histological parameters of salivary glands.	• Association between ^{18}F-FDG PET/CT (pSS subjects only), ^{11}C-MET PET/CT and MRI parameters (healthy volunteers and pSS subjects) in the region of the salivary glands with each other and with clinical measures including: – Basal and stimulated salivary flow – Histological scores from minor salivary gland biopsies including but not limited to lymphocyte count and focus score (pSS subjects) – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) • European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), in particular subcomponents relevant to salivary gland function (pSS subjects).
• To explore the extent of non-salivary gland (systemic) abnormalities detected on ^{18}F-FDG PET/CT and ^{11}C-MET PET/CT, and the association of these abnormalities with clinical scores/relevant sub-scores and laboratory biomarkers in pSS subjects.	• Semi-quantitative parameters in selected areas systemically for ^{18}F-FDG and ^{11}C-MET (including but not limited to lymph nodes, thyroid, lacrimal glands, lungs and pancreas) and the associations of these parameters with: – Laboratory biomarkers of disease activity (including metabolomic and/or proteomic profiles where applicable) – Lacrimal gland function as measured by Schirmer’s test – ESSDAI and ESSPRI and organ-specific subcomponents

	relating to the area imaged, where available.
• To compare the metabolomic profiles of pSS subjects and healthy volunteers, to assess the intra-individual variability of the metabolome over time, and the ability of samples from different bodily sites to discriminate pSS subjects from healthy volunteers.	• Compare the metabolome/proteome of pSS subjects with healthy volunteers. • Assess the variability in the metabolome and/or proteomic profile of individual subjects taken at 2 separate time points (Baseline and Visit 2). • Compare the metabolome and/or proteomic profile from different body fluids/sites, and their utility in distinguishing pSS subjects from healthy volunteers. • Samples collected will be saliva, tears and plasma.

4. STUDY DESIGN

4.1. Overall Design

Healthy volunteers will be enrolled in Group A and pSS subjects will be enrolled in Group B.

The subjects will be required to attend the clinical unit for a Screening/Baseline visit, an imaging visit (Visit 1) a sample collection visit (Visit 2) and a Follow up visit.

If Females of Reproductive Potential (FRP) are included they must have a negative pregnancy test as determined by serum human chorionic gonadotropin (hCG) test at screening, and a negative urine pregnancy test 4-7 days prior to Visit 1, and on Visit 1 (which will occur 28-42 days after screening). If Visit 1 is split over more than 1 day there must be a negative urine pregnancy test on each day, prior to scanning.

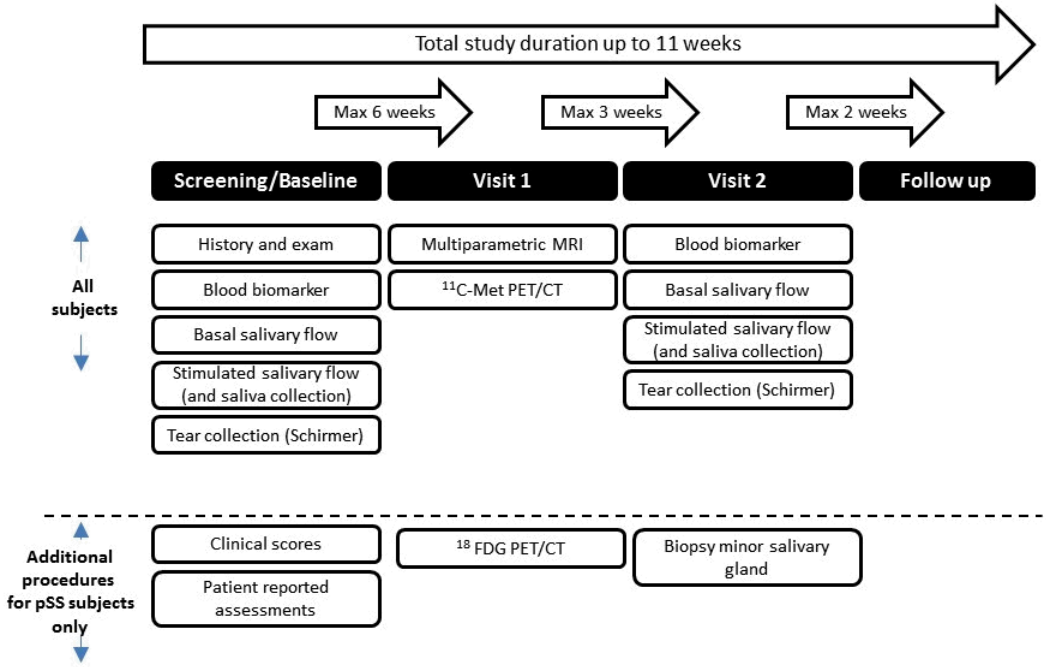
The follow up may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) will return to the clinical unit for Follow up to allow for the examination of the salivary gland biopsy site.

All assessments will be done as outpatient visits.

No investigational medicinal product (IMP) will be administered to subjects enrolled in this study.

4.2. Treatment Arms and Duration

Figure 1 Study Schematic



Screening/Baseline

Both groups of subjects will undergo a Screening/Baseline visit. At this visit, following the subject providing written consent to be enrolled on the study, the eligibility of the subjects will be assessed and baseline assessments will be performed (See Time and Events tables, Section 7.1.).

Visits

Subjects who have completed the Screening/Baseline and are eligible for the study will have an imaging visit (Visit 1).

- Group A (healthy volunteers) will undergo an MRI of the salivary glands and ^{11}C-MET PET/CT (dynamic scan of the salivary glands followed by head to hip static scan).
- Group B (pSS subjects) will undergo an MRI of the salivary glands, ^{11}C-MET PET/CT (as for Group A) and ^{18}F-FDG PET/CT (static head to hip scan).

Visit 2 will occur within 3 weeks after the completion of the assessments performed at Visit 1. The assessments will include vital signs measurement, pregnancy test (FRP only), plasma collection for the measurement of metabolomics/proteomics, measurement of basal and stimulated (chewing paraffin) salivary flow rate (including saliva collection) and Schirmer's test (including tear collection). Concomitant medication and adverse event details will be recorded.

In addition, a minor salivary gland biopsy will be performed on the pSS subjects (Group B).

Visit 1 and Visit 2 may be split over more than one day. The total duration of participation in the study will be a maximum of 11 weeks, although the visits should be completed sooner if feasible.

The details of the samples to be collected and the procedures to be performed are included in Section 7.

Follow up

Within 2 weeks of Visit 2 there will be a follow up visit. This may be conducted by telephone for the healthy volunteers (Group A). The pSS subjects (Group B) will return to the clinical unit for follow up to allow for the examination of the salivary gland biopsy site. Adverse events (AE) will be reviewed at this visit for all of the subjects (Group A and Group B)

The total duration of the study will be up to 11 weeks, although ideally the study should be completed as soon as practicable within the time windows.

4.3. Type and Number of Subjects

Between approximately 4 to 12 healthy volunteers, and between approximately 8 to 12 pSS subjects will be recruited into the study. As there is very little data about the variability of the imaging parameters, in-stream review of the variability of PET/CT and MRI data will be conducted in order to determine the number of subjects that are required for PET/CT and/or MRI (see Section 9.2.2). In order to minimize radiation exposure to healthy volunteers, a maximum of 8 healthy volunteer subjects will undergo the ^{11}C-MET PET/CT scan component.

As pSS affects females in about 90% of cases, and in order to reduce variability, initially only female healthy volunteer subjects will be recruited. If in the course of the study male pSS subjects are recruited, male healthy volunteers may be recruited at the discretion of the Sponsor. The ages of the healthy volunteers will be matched approximately to the ages of the pSS subjects as far as is practically possible, and within the age restrictions of the protocol. The procedure for approximate age matching will be described in the Study Reference Manual (SRM).

Healthy volunteers and pSS subjects will be recruited simultaneously. However, there may be some staggering in the recruitment of subjects to allow approximate age and sex matching.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor.

4.4. Design Justification

An ^{18}F-FDG-PET/CT is being used as a biomarker of inflammation to assess disease extent systemically. As ^{18}F-FDG is well characterized as a tracer, there is no need in this study to carry out this investigation in a control (healthy volunteer) group. Therefore, this investigation is restricted to the pSS subjects. In contrast there is a need to determine the kinetics and distribution of the ^{11}C-MET PET tracer in healthy volunteers and to define normal uptake of this tracer in the glands of interest, thus justifying the use of this imaging technique in the healthy volunteers. Similarly, it will be important to have control data from healthy volunteers when interpreting the DCE/DW MRI salivary gland data in the pSS subjects. Radiation exposure will be minimized by in-stream review of the variability of imaging parameters to determine the optimal sample size for each scan type.

Performing ^{18}F-FDG, ^{11}C-MET PET/CT scans, the salivary gland MRI scan as well as the minor salivary gland biopsy, laboratory biomarkers (including metabolomics and proteomics) and clinical assessments in the same pSS subject should allow assessment of associations between these endpoints. For example, in the same subject it should be possible to determine whether there are changes suggestive of salivary gland inflammation on ^{18}F-FDG-PET/CT or MRI, correlate this with the histology, and secondly to determine whether these inflammatory changes have an impact on function as determined by protein synthesis within the glands and salivary flow/symptoms. It will also be possible to understand whether there is a decrease in protein synthesis in the gland in the absence of inflammation (*eg*. inactive scarred disease). Looking at these potential associations between the imaging, histology and clinical assessments (*eg*. salivary flow) should help to determine whether they would be useful to characterize the disease in proof of mechanism studies in patients with pSS.

The study will also help to define whether there is inflammation in glandular structures or organs systemically, to correlate this with ESSDAI and subcomponents, and to assess whether gland function (protein synthesis) in these organs is impacted by any potential inflammation.

Published literature suggests there is a correlation between increased age and reduced salivary flow [Affoo, 2015], based on data from a meta-analysis of a large number of studies, and of a degree of potential relevance. Therefore, an attempt will be made to match the mean age of the healthy volunteers to the pSS subjects' where possible, whilst restricting the age range of healthy volunteers to ≥ 40 years of age.

4.5. Dose Justification

An investigational medicinal product (IMP) will not be administered to subjects enrolled in this study.

Radiaton Exposure

The total radiation exposure **for the pSS subjects** who are subjected to the studies with ^{18}F-FDG and ^{11}C-MET including its associated low-dose CT scans is expected to be **9.7mSv**, below 10mSv which falls within the Goup IIb, intermediate risk category as per the International Commission of Radiological Protection (ICRP) and generally considered ethically acceptable also for healthy volunteers *ie* 5.2mSv for the ^{18}F-FDG and associated CT, and 4.5mSv for the ^{11}C-MET components.

The healthy volunteers undergoing PET/CT will only receive ^{11}C-MET with its associated low-dose CT scans and hence be exposed to **4.5mSv**.

The average yearly radiation exposure from naturally occurring background radiation in the United Kingdom (UK) is 2.3mSv. Approval will also be obtained from the UK Administration of Radioactive substances Advisory Committee (ARSAC) prior to commencement of the study.

4.6. Benefit:Risk Assessment

The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Minor salivary gland biopsy (Group B only)	This procedure is associated with (a low) incidence of complications including discomfort, bleeding and haematoma formation.	**Subject selection:** • Subjects with bleeding disorders will be excluded from the study (exclusion # 4). • Subjects with an abnormal clotting screen or low platelet counts will be excluded from the study (exclusion #21). • Subjects who are unable to discontinue anti-coagulant medication to allow biopsy will be excluded(exclusion #16). **Subject management** • Local anaesthetic will be administered to reduce discomfort. • The biopsy will be performed by qualified physicians, surgeons or dentists with appropriate training and experience in the procedure
Subject exposed to ionizing radiation	**Radiation exposure from PET/CT scanning**: Radiation exposure from PET/CT scanning comes from two sources: the radionuclide injected for PET scanning, and the exposure to X-rays from the CT component. The estimated radiation doses for the whole study are 9.7mSv for pSS subjects and 4.5mSv for healthy volunteers. A typical diagnostic whole body CT scan would result in an exposure of around 10-15mSv.	**Study design:** 1. Low dose CT will be employed to minimize radiation exposure. 2. Subject age is restricted to ≥40 years for healthy volunteers and ≥30 years for pSS subjects to restrict radiation exposure for younger subjects (inclusion #1 and #4). 3. In stream data reviews will be performed to minimize the number of scans

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	An exposure of 9.7mSv approximates to 4 years of background radiation in the United Kingdom, and the additional risk of developing a fatal malignancy as a result of an exposure of 9.7mSv for the pSS subjects has been estimated as approximately 1 in 2100 for an adult in normal health. For healthy volunteers the total maximum effective dose of 4.5mSv is equivalent to approximately 2 times the average yearly exposure to background radiation and the additional risk of developing a fatal malignancy as a result of these exposures has been estimated at 1 in 4400 for an adult in normal health [ICRP, 2007]. To put this into context, in developed countries, the overall population risk of dying of cancer is 1 in 5 for females and 1 in 4 for males. Exposures of less than 10mSv are generally considered acceptable for research in healthy volunteers (*for discussion of potential foetal toxicity see separate section below).*	involving ionizing radiation that will be conducted
Potential radiation exposure to foetus of pregnant subject	**Ionizing radiation from CT scans and PET tracers** The potential risks of concern from foetal exposure to ionizing radiation are non-cancer adverse effects (*eg* miscarriage, malformation), and risks of childhood cancer. If for any reason a pregnant subject is	**Study design:** • Pregnant females are not eligible for the study (inclusion # 9). • Female subjects considering the study will be advised about the need to avoid pregnancy during the study until Follow up, and about the contraceptive and pregnancy testing requirements of the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	scanned, radiation exposure to the foetus from the whole study would be in the order of 10mGy or less for the pSS subjects, and lower for healthy volunteers. No non-cancer foetal adverse effects of radiation exposure (*eg* miscarriage, foetal malformation) have been detected below 50mGy exposure. For a foetus exposed in utero to 10mGy of radiation, the absolute risk of cancer at ages 0-15 years of age is about 1 excess cancer death per 1700 exposed (Annals of the IRCP, Volume 30, 1, 2000 (ICRP, 2000).	study before consent. • Females of reproductive potential will be required to use highly effective methods of contraception (as specified in the protocol) for 30 days prior to Visit 1 until Follow up. **Subject monitoring and management:** • Females of reproductive potential will undergo pregnancy testing to exclude pregnancy prior to scanning as described in inclusion #9. • **Withdrawal criteria:** In the event of a pregnancy in a female subject in the study, the subject will be withdrawn.
Subject exposed to gadolinium containing MRI contrast agents	The study uses DOTAREM (gadoterate meglumine) as an MRI contrast agent. **Non clinical data (source: gadoterate meglumine Summary of Product Characteristics (SPC)** The recommended clinical dose is 0.1mmol/kg (*ie* 0.2mL/kg). The administration of DOTAREM in rats and in dogs at daily doses up to 3mL/kg (*ie* 15 times the dose laid down in clinical conditions) and for 28 days cause no other effect than a reversible vacuolisation of the proximal tubular cells of the kidney.	**Subject selection:** • Subjects with impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/minute/1.73m^2) are excluded by the eligibility criteria (exclusion #20). • Subjects with a history of sensitivity to gadoterate meglumine containing contrast agents will be excluded from the study (exclusion #18). The site(s) will be responsible for following any additional safety guidelines for the specific gadoterate meglumine containing contrast agent used at the site and not scan

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Preclinical studies have demonstrated that DOTAREM is non-toxic for gestating females, non embryo-toxic and non teratogenic for the foetus. No prior peri- and post-natal toxicity and fertility studies have been carried out (source: SPC). **Clinical data:** Use of MRI contrast agents in subjects with severely impaired renal function Glomerular Filtration Rate (GFR) <30mL/minute has been associated with Nephrogenic Systemic Fibrosis (NSF)] (this is a class risk rather than specific for this particular agent). In subjects with severely impaired renal function, the benefits of the use of contrast agents should be carefully weighed against the risks. Gadolinium (Gd) contrast agents can be associated with anaphylactoid or hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular respiratory or cutaneous manifestations, and ranging to severe reactions including shock. The risk of hypersensitivity reactions may be higher in case of previous history of reactions, bronchial asthma and history of allergic disorders. Most of these reactions occur within half an hour of administration. Delayed reactions (after hours or several days) have been rarely	subjects if contra-indicated(exclusion #19). **Subject monitoring and management** • The MRI procedure will be conducted under the supervision of trained and qualified clinical staff who are trained to appropriately manage an allergic reaction. • MRI contrast at a dose less than or equal to 0.1mmoL/kg will be used. If it is necessary for technical reasons to repeat the MRI (no more than once), gadolinium contrast administration will not be repeated within a 24 hour period. *For pregnancy risk mitigations please see section above (potential radiation exposure to foetus of pregnant subject).*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	observed	
Subject exposed to a high field MRI magnet	Certain prostheses or foreign bodies might be incompatible with the MRI scanner	**Subject selection:** All participants will be screened according to local scanner criteria and trial inclusion/exclusion before entering the MRI room to ensure they are able to have the MRI conducted. Subjects with non-MR compatible metal implants or implantable electronic devices (*eg* pacemaker, defibrillator) will not be included in the study (exclusion #8).
Administration of PET tracers ^{18}F-FDG and ^{11}C-METhionine (including potential risks to a fetus of a pregnant subject)	**^{18}F-FDG PET Tracer:** Nonclinical data: Toxicological studies with a single intravenous (IV) injection of ^{18}F-FDG at 50-fold human dose in dogs and 1000-fold human dose in mice have not identified potential risks of clinical significance. **^{11}C-MET PET tracer** Methionine is an essential amino acid that is not synthesized *de novo* in humans, who must ingest methionine or methionine containing proteins. The daily adult requirement of methionine is 10mg/kg [Protein and amino acid requirements in human nutrition. Report of a joint Food and Agriculture Organization of the United Nations (FAO)/ World Health Organisation (WHO)/ United Nations University (UNU) expert consultation [WHO, 2007]. The dose	**Study design:** • The ^{11}C-MET will be produced according to Good Manufacturing Practice (GMP), and the specifications in the European Union (EU) Pharmacopoeia. • ^{18}F-FDG is purchased from a commercial producer, in accordance with product labelling. • The radiotracers will be administered at doses according to product labelling (where available) and the EU Pharmacopoeia. • Staff handling the tracers will have the necessary training and authorizations in their use. • For pregnancy risk mitigations please see section above (potential radiation exposure to foetus of pregnant subject).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	administered is several hundred fold less than the recommended daily intake of this essential amino acid. It is not anticipated that there will be any risks (reproductive or other) of the molecule itself (excluding ionizing radiation), although no foetal reproductive toxicity data is available	

4.6.2. Benefit Assessment

This study does not involve the use of an investigational medicine; therefore, participation will provide no therapeutic or direct medical benefit to participating individuals. However, it is anticipated that the data collected from this investigation will improve understanding of the relationship between structure, function and inflammation in pSS. Furthermore, subjects completing the study will potentially aid future improvement of the quality of care of pSS subjects by contributing to the development of improved imaging methods.

4.6.3. Overall Benefit:Risk Conclusion

Based upon the safety strategies and risk mitigations inherent to this protocol, GlaxoSmithKline (GSK) concludes the Benefit:Risk for a subject's participation in the GSK study 203818 is adequate and supports the study conduct.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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:

GROUP A: Healthy Volunteers

AGE
1. **Subjects for both PET/CT and MRI**: Aged >=40 years inclusive at the time of signing the informed consent. 2. **Subjects for MRI, without PET/CT**: Aged >=30 years inclusive at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
3. Healthy as defined by the investigator, or medically qualified designee, based on a medical evaluation including medical history, physical examination, and laboratory tests. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion/exclusion criteria may be included only if the investigator in consultation with the GSK Medical Monitor, if required, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

GROUP B: Primary Sjögren's Syndrome Patients

AGE
4. Age >=30 years, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
5. Diagnosis of primary Sjögren's Syndrome according to the American-European Consensus Group criteria [Vitali, 2002]. 6. Baseline unstimulated salivary flow >0.0mL/min or evidence of glandular reserve function (stimulated baseline salivary flow >0.05mL/min). 7. Systemically active disease, ESSDAI >=5 points.

All Subjects

WEIGHT
8. Body weight >=50 kg and body mass index (BMI) within the range 18.5 to 35 kg/m^2 (inclusive).

SEX
9. Male or Female, where one of the following conditions apply: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test) at screening, and a negative urine pregnancy test 4-7 days prior to Visit 1, on the day of Visit 1 (on each day of scanning), on Visit 2, is 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 use a male condom PLUS one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP), Section 12.3 (Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information) from at least 28 days prior to Visit 1, until after the completion of the follow-up visit. • The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
10. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF).

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 (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Diagnosis of secondary Sjögren's Syndrome. 2. Diagnosis of another systemic autoimmune disease, apart from pSS, including but not limited to, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis or systemic vasculitis. For Group B subjects, autoimmune conditions associated with pSS (for example autoimmune thyroiditis, primary biliary cirrhosis or coeliac disease), are not included in this exclusion, but should be described in the medical history taken baseline. If in doubt please consult the medical monitor. 3. Subjects with active life-threatening or organ-threatening effects of pSS meaning that they may not be able to complete the study visits according to the protocol (as determine by the investigator) (Group B). 4. History of coagulation or bleeding disorders which would increase the risk of minor salivary gland biopsy (for example but not limited to Haemophilia A or B, Von Willibrand's disease, platelet function disorders) (Group B). 5. History of malignancy within 5 years of screening that, in the view of the investigator, in consultation with the medical monitor if required, could confound the results of the ^{18}F-FDG PET/CT scan (including lymphoma associated with pSS). This does not include cervical carcinoma in situ or non-melanoma skin malignancy that has been treated with curative surgical treatment. 6. History of unresolved acute or chronic infection that, in the view of the investigator in consultation with the medial monitor, if required, could confound the results of the ^{18}F-FDG PET/CT. 7. Subject has diabetes mellitus requiring insulin therapy.

8. Contraindications to MRI scanning (as assessed by MRI safety questionnaire).
9. History of, or suffers from, claustrophobia or feel that they will be unable to lie still in the PET or MRI scanner for a period of up to 1 to 2 hours.
10. Where participation in the study would result in donation of blood or blood products in excess of 500mL within a 56 day period.
11. Previous inclusion in a research protocol involving nuclear medicine, PET or radiological investigations, or as a result of occupational exposure with a significant radiation burden (a significant radiation burden being defined as 10mSv in addition to natural background radiation, in the previous 3 years including the dose from this study). A clinical procedure where the subject received a direct benefit (eg diagnostic test) will not be included in the calculation of exposure.
12. Lack of adequate peripheral venous access for cannulation.
13. Current participation in a study with an investigational product, or recent participation within 5 half lives of discontinuation the drug, or within twice the duration of the biological effect of the drug, whichever is longer.

CONCOMITANT MEDICATIONS

14. Group A: healthy volunteers. Subject is unable to refrain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days prior to Visit 1 until completion of Visit 2, unless in the opinion of the investigator and Sponsor the medication will not interfere with the study.
15. Group B- pSS subjects taking immunomodulatory treatment at screening are excluded unless they have been on stable doses of these medicines for 6 weeks prior to Screening/Baseline and are expected to remain on stable doses of these medications until the Follow up visit. This would include drugs such as glucocorticoids, immunosuppressive agents (for example hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, and biologic therapies). Permitted medications are listed in Section 6.8. If in doubt please discuss with the Medical Monitor.
16. Group B: pSS subjects. Receiving treatment with anti-coagulant medications, including but not limited to warfarin, heparin, thrombin inhibitors, and Factor Xa inhibitors, and aspirin, unless the subjects is able to discontinue these medications one week prior to minor salivary gland biopsy, or according to local guidelines. The treatment may be restarted 3 days after the biopsy, or according to local guidelines.

RELEVANT HABITS

17. History of alcohol, prescription or non-prescription drug abuse which could interfere with participation in the trial according to the protocol, or in the opinion of the investigator impacts on the physical or mental wellbeing of the subject.

CONTRAINDICATIONS

18. History of allergy/hypersensitivity to study medications including local anaesthesia (Group B), radio-isotopes or gadolinium-containing contrast agents (all subjects).
19. Contraindications to gadolinium-containing contrast agents in accordance with

product labelling and local guidelines.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
20. Estimated GFR [Modification of Diet in Renal Disease (MDRD) calculation] of less than 60mL/min/1.73m^2 at screening.
21. Platelet count below the laboratory normal range at screening, or prothrombin time above the laboratory normal range at screening (Group B).
22. Subject with a fasting blood sugar >11.1mmol/L at screening (defined as fasting for a minimum of 6 hours, excluding unflavoured water).

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 failure subjects meets the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (SAE) (see Section 7.3.1.4).

Subjects that are not enrolled into the study within the allotted screening window may be re-screened once. If re-screening is performed, subjects are assigned a different unique subject ID number for the re-screening, and all screening procedures must be repeated. See the SRM for specific details.

5.4. Withdrawal/Stopping Criteria

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.
- The subject becomes pregnant.
- The subject develops an allergic reaction to imaging contrast agents or any study administered treatments (radio-isotope, gadolinium, local anaesthesia), including anaphylaxis.
- The subject experiences a clinically significant severe AE or SAE that has a reasonable possibility of being related to study procedures.
- The study is discontinued by the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the site 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 the subject wishes to 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".

5.4.1. Liver Chemistry Stopping Criteria

There is no IMP in this study therefore there are no liver chemistry stopping or increased monitoring criteria.

5.4.1.1. Study Treatment Restart or Rechallenge

Not Applicable

5.4.2. QTc Stopping Criteria

There is no IMP in this study therefore there are no QTc stopping criteria for this study.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the Follow up.

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

6. STUDY TREATMENT

6.1. Investigational Product or other Study Treatment

There is no IMP in this study. Imaging agents are listed in Table 1.

Table 1 Study Treatments

	Study Treatment		
Product name: (Generic name and trade)	^{18}F-FDG (Group B only)	^{11}C-MET	Gadoterate meglumine (Dotarem)
[Formulation description:]	Refer to the summary of product characteristics (SmPC).	In accordance with EU Pharmacopoeia.	Refer to SmPC.
Dosage form:	Refer to SmPC.	Refer to study procedures manual (SRM)	Refer to SmPC.
Unit dose strength(s)/Dosage level(s):	200MBq.	500MBq.	Dose less than or equal to 0.1mmol/kg
Route of administration	For IV injection	For IV injection	For IV injection
Dosing instructions:	Refer to SmPC	Please refer to SRM	Please refer to SmPC
Physical description:	Refer to SmPC	Refer to SmPC	Refer to SmPC
Method for individualizing dosage:	None	None	Dose on mg/kg basis.

6.2. Blinding

This will be an open-label study.

6.3. Packaging and Labelling

^{18}F-FDG and DOTAREM will be purchased from commercial suppliers. ^{11}C-MET will be produced by Imanova, and the contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

Imaging agents will be prepared, handled and stored according to product labels, where available, and applicable regulatory requirements.

6.5. Treatment of Study Treatment Overdose

Imaging agent overdose will be managed according to product labels, where available, and local SOPs.

6.6. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because no medicinal products are being investigated in this study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

6.7. Lifestyle and/or Dietary Restrictions

- Subjects should refrain from alcohol in the 24 hours prior to all study visits.
- Subjects will be asked to eat a meal prior to the ^{11}C-MET scan in order to stimulate salivary gland function (details in SRM). Subjects should advise of any dietary restrictions so that a suitable meal can be organised (or if necessary can bring their own food by arrangement).
- Group B (pSS) patients will be asked to fast (with the exception of unflavoured water), for a minimum of 6 hours prior to the ^{18}F-FDG PET/CT scan.
- At the Screening/Baseline visit and Visit 2, the following restrictions apply, until after the collection of tears, saliva and plasma samples:
  - Subjects should fast for a minimum of 6 hours (with the exception of unflavoured water) until after sample collection.
  - Subjects will be required to withhold dosing with oral muscarinic agonists (such as pilocarpine and cevimiline) in the 12 hours prior to the Screening/Baseline visit and Visit 2.
  - For at least 2 hours prior to saliva collection, subjects should not brush their teeth or use oral hygiene products (including saliva substitutes or oral gels) or chewing gum, and not smoke.
  - Subjects should not use topical eye drops for 2 hours prior to tear collection until after tear collection.
  - Not apply eye makeup on the day of the visits, until after the tear collection.
  - Not wear contact lenses on the day of the visits, until after the tear collection.

6.7.1. Contraceptive Requirements

6.7.1.1. Female Subjects

Refer to eligibility criterion number 9 and Section 12.3 (Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information). The allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

6.7.1.2. Male subjects

There are no contraceptive requirements for male subjects in this study.

6.8. Concomitant Medications and Non-Drug Therapies

6.8.1. Permitted Drug Therapies (Group B: Primary Sjögren's Syndrome Subjects)

- Stable doses of potentially immunomodulatory treatments are permitted (stable from 6 weeks prior to screening until follow up). This includes potentially disease modifying drugs such as glucocorticoids, immunosuppressive agents (*eg* hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, and biologic therapies). The investigator should discuss drug therapies with the Medical Monitor if they have any safety concerns or are unsure about the potential impact on the scientific validity of the study data.
- Topical symptomatic therapies (such as [a] non-medicated ocular topical drops: saline or glucane; [b] non-pharmacologic oral topical agents: chewing gum, saliva substitutes) are permitted. Subjects will be required to withhold dosing with these agents in the 2 hours prior to collection of saliva and tear samples at Screening/Baseline visit and Visit 2.
- Oral muscarinic agonists (such as pilocarpine and cevimiline) are permitted. Subjects will be required to withhold dosing with these agents in the 12 hours prior to the Screening/Baseline visit and Visit 2.
- Anticholinergic agents, such as tricyclic antidepressants, buproprion, antihistamines, phenothiazines, antiparkinsonian drugs, anti-asthmatic medications, or gastrointestinal medications that cause xerostomia in more than 10% of patients are permitted provided that a subject is on a stable regimen for at least 4 weeks prior to Screening/Baseline visit until follow up has been completed.

6.8.2. Prohibited Medications and Non-Drug Therapies

Group A: Healthy Volunteers

- Healthy volunteers are to refrain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days prior to Visit 1 until after Visit 2, unless in the opinion of the investigator and Sponsor the medication will not interfere with the study.

Group B: Primary Sjögren's Syndrome Subjects

- Treatment with anti-coagulant medications, including but not limited to warfarin, heparin, thrombin inhibitors, and Factor Xa inhibitors, and aspirin, unless the subjects are able to discontinue these medications one week prior to minor salivary gland biopsy (Visit 2), or according to local guidelines. The treatment may be restarted 3 days after the biopsy, or according to local guidelines.

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 tables, is 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 Table 2 and Table 3

The change in timing or addition of time points for any planned study assessments must be documented in a Note to File approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Table 2 Time and Events Table – Screening and Baseline Assessments

Procedure	Screening/Baseline Visit	Baseline 2 (FRP only)
		Within 4-7 days prior to Visit 1
Informed consent	X	
Inclusion and exclusion criteria	X	
Demography	X	
Medical history including past and current medical conditions	X	
Full physical exam (including height and weight)	X	
MRI safety questionnaire	X	
Vital signs	X	
Concomitant medication review	X	
ESSDAI	X[1]	
ESSPRI	X[1]	
Oral dryness numerical rating	X[1]	
Ocular dryness numerical rating	X[1]	
Patient global assessment	X[1]	
Physician's global assessment	X[1]	
Basal salivary flow	X	
Stimulated salivary flow (including saliva collection)	X	
Schirmer's test (including tear collection)	X	
Plasma metabolomics/proteomics	X	
Haematology/clinical chemistry [see Table 4]	X	
Blood biomarkers for ESSDAI [see Table 4]	X[1]	
Autoantibody screen (anti-Sjögren's-syndrome-related antigen A [Anti-SSa], anti Sjögren's syndrome type B [SSb])	X[1]	
FSH/oestradiol (post-menopausal women only)	X	
Serum pregnancy test (FRP)	X[2]	
Urine pregnancy test(FRP)		X[2]
Urinalysis	X[3]	

AE = adverse event; FSH = follicle stimulating hormone; MRI = magnetic resonance imaging; FRP = females of reproductive potential; .ESSDAI = European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index; ESSPRI =EULAR Sjögren's Syndrome Patient Reported Index

1. pSS subjects only
2. Females of reproductive potential only.
3. Urine to be sent for urine protein:creatinine ratio if ≥trace proteinuria by dipstick.

Table 3 Time and Events Table – Study Assessments

Procedure	Visit 1	Visit 2	Follow up
	Within 6 weeks after baseline (4-6 weeks for FRP)	Within 3 weeks after Visit 1	Within 2 weeks after Visit 2
MRI safety questionnaire[5]	X		
Vital signs	X	X	
Concomitant medication review	X	X	
Basal salivary flow		X	
Stimulated salivary flow (including saliva collection)		X	
Schirmer's test (including tear collection)		X	
Plasma metabolomics/proteomics		X	
Urine pregnancy test (FRP)	X[1]	X[1]	
Multi-parametric MRI scan (including contrast)	X		
Meal prior to ^{11}C-MET PET/CT	X		
Intravenous injection of ^{11}C-MET PET tracer	X		
^{11}C-MET PET/CT scan (dynamic and static)	X		
Radio-PK (^{11}C-MET) sampling (dynamic scan)	X[2]		
Measure concentration of ^{11}C-MET tracer in blood	X[3]		
Blood glucose (bedside glucometer)	X[4]		
Injection of ^{18}F-FDG tracer	X[4]		
^{18}F-FDG PET/CT scan	X[4]		
Measure concentration of ^{18}F-FDG in blood	X[3,4]		
Salivary gland biopsy		X[4]	
AE review	X		

AE = adverse event; CT = computed Tomography; FDG = flurodeoxyglucose; FRP = females of reproductive potential; FSH = follicle stimulating hormone; MET = methionine; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics;.

1. Females of reproductive potential only
2. Radio-PK sampling (5mL per sample) to be taken at 1, 2, 5, 10, 15, 20, 30 and 40 minutes after injection of ^{11}C-MET PET tracer (number and sampling times are subject to change dependent on emerging data, but no more than 100 mL overall will be taken).
3. To be taken within 5 minutes after the static PET/CT scan (exact time to be recorded).
4. pSS subjects only
5. The MRI safety questionnaire will not be databased

7.2. Screening and Critical Baseline Assessments

7.2.1. For all subjects:

Information collected during the Screening/Baseline assessments described below represents key data that identifies and defines subject baseline status. This information is critical for the evaluation and comparison of subsequent imaging assessments. Additional assessments will be performed as detailed in the Time and Events tables, Table 2 and Table 3.

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 undergo screening assessments within 42 days (28-42 days for FRP) prior to Visit 1. At screening 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 5.1 and Section 5.2. 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. 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 (where applicable, for Group A or Group B):

- Past or current conditions, including Sjögren's syndrome history.
- 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 (requiring inpatient treatment, 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).

Serum and urine pregnancy test: A test will be performed for women of child-bearing potential at Screening/Baseline. A urine pregnancy test will be repeated 4 to 7 days prior to Visit 1.

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.

Urinalysis: will be performed as related to the eligibility criteria listed in Section 5.1 and Section 5.2.

In addition, urinalysis will be performed in subjects included in Group B in order to calculate the ESSDAI score. If proteinuria is detected on dipstick (≥trace), quantification of the spot urine protein:creatinine ratio will be needed in the laboratory to calculate the ESSDAI score.

Haematology (including coagulation screen) **and blood chemistry (clinical safety laboratory assessments):** will be performed as related to the eligibility criteria listed in Section 5.1 and Section 5.2.

Female subjects:

FSH and oestradiol (females of non-reproductive potential only).

Serum hCG (at screening only) and urine hCG pregnancy test at other times as required (for females of reproductive potential).

Estimated Glomerular filtration rate (eGFR): will be calculated using the modification of diet in MDRD formula.

Unstimulated and stimulated salivary flow: Salivary flow rate will be assessed as an eligibility criterion for pSS subjects and a baseline procedure for all subjects. Subjects with 0.0mL/min unstimulated salivary flow rate may qualify for the study if their stimulated salivary flow is greater than 0.05mL/min. Details of the collection procedure will be further specified in the SRM.

Schirmer's test: This is an assessment of lacrimal gland function as a baseline procedure 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.

MRI safety questionnaire: in order to confirm eligibility for the MRI scan.

7.2.2. Additional baseline procedures for Group B subjects only (pSS Subjects)

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.

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 investigator. 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, 2014].

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 to 10 Numeric Rating Scale (NRS) for each symptom. The ESSPRI assessment tool will be detailed in the SRM.

Blood biomarkers (in order to confirm diagnosis and to calculate ESSDAI score: Quantification of serum autoantibodies (including anti-SS-A, SS-B), and immunological testing required for ESSDAI (including serum immunoglobulins [Total Immunoglobulin (Ig), IgG, IgA, IgM], protein electrophoresis, complement C3, C4 and C-reactive protein). Cryoglobulin testing is only needed if required for the calculation of ESSDAI score.

Oral and Ocular Dryness: will be reported by subjects on a numerical rating scale from 0 to 10. A description of the instrument anchors and technique for administering these scales will be described in the SRM.

Physician global assessment of disease activity: the Physician Global Assessment is a physician 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.

Patient global assessment of disease activity: 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.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events tables (Table 2 and Table 3). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE and SAE can be found in Section 12.2.

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

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (*eg* protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.
- AEs will be collected from Visit 1 until the follow up contact (see Section 7.3.1.4), at the time points specified in the Time and Events Tables (Table 2 and Table 3).

- Medical occurrences that begin prior to Visit 1 but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.2 (Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow up and Reporting of Adverse Events).
- 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 2.

7.3.1.2. 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?"

7.3.1.3. 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 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). Further information on follow up procedures is given in Section 12.2 (Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow up and Reporting of Adverse Events).

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) 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. An IMP will not be administered to the subjects in this study. GSK will comply with country

specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/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 (*eg* summary or listing of SAEs) from GSK will file it with the Investigator Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

Details of all pregnancies in female subjects will be collected from Visit 1 and until follow up.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 12.3 (Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information).

7.3.3. Vital Signs

Single assessment of vital signs will be performed at the times indicated in the Time and Events Tables (Table 2 and Table 3). Vital signs will be measured in the semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.

7.3.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4 must be conducted in accordance with the Laboratory Manual, and the Protocol Time and Events Schedule (Table 2 and Table 3). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation of samples are detailed in the SRM.

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 (*eg* SAE or AE) the results must be recorded in the CRF.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	*Full blood count indices*	*Red blood cell count Indices*:	*White blood cell count with Differential:*	
	White blood count	Mean corpuscular volume (MCV)	Neutrophils	
	Platelet Count	Mean corpuscular haemoglobin	Lymphocytes	
	Haemoglobin	Mean corpuscular haemoglobin concentration	Monocytes	
	Haematocrit		Eosinophils	
	Coagulation screen		Basophils	
	Prothrombin time, Activated partial thromboplastin time Thrombin time			
Clinical Chemistry	Urea	Potassium	Aspartate aminotransferase	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Total Protein
	Glucose (fasting for 6 h [excluding unflavoured water])	Calcium	Alkaline phosphatase	Albumin
	Creatine kinase	C-reactive protein		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal) and send urine for spot urinary protein:creatinine ratio			
Other Screening Tests	• Follicle-stimulating hormone and oestradiol (as needed in females of reproductive potential only) • Serum human chorionic gonadotropin (hCG) [at screening only] and urine hCG pregnancy test (as needed for females of reproductive potential) • **Group B only:** anti-Sjögren's-syndrome-related antigen A (Anti-SSa), anti-Sjögren's syndrome type B (SSb), total immunoglobulin (Ig), IgG, IgA, IgM, serum protein electrophoresis, complement C3, C4 • **Optional additional tests in Group B (if needed for calculation of ESSDAI):** cyroglobulins, urinary protein creatinine ratio (if dipstick ≥trace protein).			

	• Estimated glomerular filtration rate will be calculated using the modification of diet in renal disease (MDRD) formula.
NOTES : European League Against Rheumatism (EULAR) primary Sjögren's syndrome disease activity [ESSDAI]	

Safety laboratory tests are only conducted at screening in this study. Subjects with values that are considered clinically significantly abnormal will be assessed according to the inclusion/exclusion criteria. In the event of clinically significant laboratory values the investigator will advise the subject of appropriate clinical care.

7.4. Imaging Procedures

7.4.1. PET Imaging Procedure

Positron Emission Tomography scans will be acquired on a PET/CT scanner at the imaging centre. The details of the PET imaging procedure, image processing and analysis will be provided by the imaging centre in a PET Imaging Manual.

Subjects will be given a meal before the ^{11}C-MET tracer injection to stimulate salivary gland function.

Prior to the commencement of the PET scan a venous cannula will be inserted into the subjects arm for administration of ^{18}F-FDG or ^{11}C-MET. An additional venous cannula will also be inserted prior to the scan start from which blood samples will be collected at the time points described in the Time and Events tables Table 2 and Table 3. The subject will be positioned in the scanner and sufficient padding will be used to minimize movements during image acquisition. The subject will be monitored continuously by a qualified PET technician.

For ^{11}C-MET PET scanning, a low-dose CT attenuation scan centred on the salivary glands will be performed for subsequent attenuation and scatter correction of the PET data. Thereafter, the PET scan will commence with an intravenous bolus administration of ^{11}C-MET (500 MBq) and dynamic scanning of the salivary gland region for approximately 40 minutes. The static scan will follow (within approximately 5 minutes) with the whole body CT followed by the PET covering the head to hip with a duration of same range for approximately 20 to 30 minutes.

For ^{18}F-FDG PET scanning, scanning will start 60 minutes after intravenous bolus administration of 200 MBq of ^{18}F-FDG. Blood glucose (bedside glucometer) will be measured before injection of ^{18}F-FDG tracer. If the glucometer blood glucose is greater than 11.1mmol/l, the ^{18}F-FDG cannot be injected, and it will be necessary to reschedule the scan. Advice for Investigators regarding diabetics on oral hypoglycaemic agents will be described in the SRM, and the scan will be scheduled in the morning for these subjects wherever possible. Firstly, a low-dose CT attenuation scan of the area to be scanned (head to hip) will be performed. Thereafter, the PET scan will commence with static scanning acquired for up to 30 to 40 minutes.

After the PET scans, a blood sample will be taken for measurement of radioactivity in blood and plasma (See Section 7.6).

After the scan the subjects will be allowed home at the discretion of clinical staff at the imaging facility.

7.4.2. MRI Imaging Procedure

As part of the study, eligible subjects will undergo multi-parametric MRI scanning, including administration of a gadolinium based contrast agent at the imaging centre to assess salivary gland inflammation, function and structure in pSS subjects and healthy volunteers. Additionally, the images may be used to identify and delineate the anatomical Regions of Interest (ROI) for individual PET images and to aid in image analysis.

On attendance at the MRI department, subjects will be placed in the scanner and will be prepared for intravenous contrast agent administration. The scanning protocol will include routine localizers, T1 measurement sequences, DCE-MRI acquisition, DW-MRI acquisition, and additional exploratory MRI endpoints, as detailed in the Imaging Acquisition Manual. The total scan time should not exceed 1 hour.

If a scanning failure occurs, if feasible a rescan is allowed within 7 days after the failed scan. There will be a minimum of 24 hours between scans where gadolinium contrast is used.

7.5. Image Analysis

All MRI and PET scans will be available at site, and will be reported at the site by a radiologist for clinical abnormalities per local standard procedures. If a significant clinical abnormality is identified that requires further investigation, the Investigator will be informed such that they can arrange appropriate investigations and medical care of the subject.

7.5.1. PET Image Analysis

Following reconstruction, scatter correction and attenuation correction, the PET data will be corrected for motion (if required) and if possible co-registered to each subject's structural MRI image. Anatomic regions of interest (ROIs) will be defined using a combination of each subject's PET/CT and MRI. Those ROIs will then be applied to the PET emission data to derive decay-corrected regional time-activity curves.

For the static head to hip ^{18}F-FDG and ^{11}C-MET scans, semi quantitative imaging outcome parameters (including standardized uptake value) will be generated from the decay corrected single time point activity measurement.

The primary structures to be included in the analysis include the different salivary glands, lymph nodes and pancreas whenever feasible with respect to size and signal intensity. Specific areas of increased FDG uptake in different areas of the body, for example including but not limited to the lungs will also be recorded and measured when possible.

Regions in normal structures like liver and blood pool in aorta may be included.

For the dynamic ^{11}C-MET scan, a radiometabolite-corrected plasma input function will be generated for each subject. The decay corrected time-activity curves will be analysed using a range of kinetic models including compartmental models and reference tissue models if a valid reference region is available in the field of view of the scan. The primary image outcome parameters will depend on the kinetics of the tracer in the region of interest and will be decided using quantitative criteria of model selection.

7.5.2. MRI Image Analysis

Reconstructed MR images for the various sequences will first be corrected for geometric distortion and subject motion, as needed and appropriate. Quality assurance procedures may be followed to assert image-characteristic consistency over the course of the study. These procedures may include checks on imaging metadata, as well as checks on the image data itself. Anatomical ROIs will be defined on structural MR imaging for salivary glands including both parotids glands and other major salivary glands if possible.

For the gadolinium enhanced perfusion sequence, a multiparametric model will be fitted for subject and for each point in the anatomical ROIs. This model will describe the wash-in of contrast medium following injection, the efflux of contrast medium from the capillaries to the extravascular space, and finally the wash-out of the medium from the tissue. The parametric maps obtained from the model, including maps for Ktrans, IRE and ME may then be used to calculate aggregate measurements per ROI.

Similarly, imaging data for the diffusion sequence will also be used to fit a multiparametric model. This model will describe the total diffusion of water as a composition of pure water diffusion and pseudo diffusion, *ie* the incoherent motion of water molecules due to capillary blood flow. Again, parametric maps, including maps for ADC, D and f may be used to compute aggregate measurements for each of the ROIs.

To investigate the complimentary relation between both imaging models, various combined models may be explored. This may include model based approaches such as alternative diffusion models that are informed by the tracer kinetic DCE model, but may also include data driven approaches such as higher level statistical analyses that are based on the parametric maps of both primary models.

These complimentary models are exploratory, but have the potential to generate outcome measures for future trials.

7.6. Pharmacokinetics

7.6.1. Blood sample collection and ^{11}C-Met radio PK analysis

Blood sample collection and analysis will be performed at Imanova Ltd.

Static ^{18}F-FDG and ^{11}C-MET acquisitions: At the end of each PET/CT scan, a single venous blood sample (3 mL) will be acquired for determination of whole blood and plasma radioactivity concentration.

Dynamic ^{11}C-MET acquisition: During the dynamic ^{11}C-MET PET acquisition, venous blood samples will be collected. Blood will be drawn in 5mL volumes at 1, 2, 5, 10, 15, 20, 30 and 40 minutes after injection of PET tracer. Sampling times and number of samples are subject to change, dependant on emerging data, but no more than 100 mL overall will be taken. The details of the time windows for the collection of these blood samples will be included in the SRM.

Tracer radioactivity concentration will be measured in plasma and whole blood, using a counter previously cross-calibrated with the scanner. In addition, metabolite analysis will be conducted on the plasma samples via High Performance Liquid Chromatography (HPLC). The timing of pharmacokinetics (PK) samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. In all instances, the actual time of each blood sample collection will be recorded. Blood samples collected during PET/CT imaging will be analysed immediately, and will not be stored. Processing and storage procedures are provided in the SRM.

7.7. Salivary gland biopsy (Group B)

A minor salivary gland biopsy will be performed on Visit 2 (pSS subjects only). The salivary gland biopsy surgical technique and sample handling will be described in the SRM and a training video will be made available with details of the procedure. Biopsy tissue will be shipped to a histopathology laboratory for processing and assessment. Histological assessments performed on salivary gland tissues will be conducted as described in Section 7.8.1.3.

7.8. Biomarker(s)/Pharmacodynamic Markers

7.8.1. Novel Biomarkers

7.8.1.1. Metabolomic Research

Biofluid (saliva, tears and plasma) metabolome studies may be performed by nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS, Liquid Chromatography [LC]-MS, Gas Chromatography [GC]-MS and/or Fourier Transform [FT]/MS) and/or equivalent methods. This may be done to compare the metabolome of pSS subjects with healthy volunteers, as well as to assess the variability in the metabolome and/or proteomic profile of individual subjects taken at 2 separate time points (Baseline and Visit 2). A comparison of the metabolomic and/or proteomic profile from different body fluids (saliva, tears and plasma), and their utility in distinguishing pSS subjects from healthy volunteers may also be investigated. Associations between the metabolome data with proteomic data, clinical, serum biomarker, histological and imaging parameters may be studied.

7.8.1.2. Proteome Research

Biofluid (saliva, tears and plasma) proteome studies may be performed by 2-D gel separation, and/or peptide mass mapping, or an alternative equivalent procedure. These differentially expressed proteins may be identified by mass spectrometry or equivalent technology. Intra-subject variability may be assessed by comparing the proteomic profile

of individuals at two different time points (Screening/Baseline and Visit 2). Comparisons may be made between the proteomic profiles of pSS subjects and healthy volunteers. Association of the observed proteomic parameters with clinical, imaging and immunological, serum biomarker, metabolome and histological parameters may be performed. Samples for longitudinal analysis will be collected and stored as described in the SRM and may be analysed at the end of the study.

The same samples may also be used to confirm findings by application of alternative technologies.

7.8.1.3. Salivary gland histological assessment

Histological assessments of salivary gland tissue will include a determination of lymphocyte infiltrate by Immune Histochemistry (IHC) (B and T cell subsets) and assessed through haematoxylin and eosin staining for foci scoring. The IHC assessment may include, (but not be limited to): B cell markers: CD20, IgG, IgM, IgA and CD38; T cell markers: CD3; markers of germinal centre formation: CD21 and markers of dividing cells: Ki67. Confocal microscopy or other specialist imaging techniques may be employed to image immunofluorescence stained sections.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined 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 Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.
- Case report forms (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to explore the use of ^{18}F-FDG PET/CT, ^{11}C-MET PET/CT, and multi-parametric MRI in pSS subjects and/or healthy volunteers. Due to the exploratory nature of this study, there are no formal hypotheses being tested.

For ^{11}C-MET PET/CT and multi-parametric MRI, summary statistics will be used to interpret each derived parameter. An exploratory comparison of pSS subjects vs healthy

volunteers may performed for each ^{11}C-MET PET/CT and multi-parametric MRI derived quantitative parameter as data permits, to estimate difference (or ratio if log transformation is needed) with 95% confidence interval.

For ^{18}F-FDG PET/CT where only pSS subjects will be scanned, summary statistics will be used to present each derived parameter.

9.2. Sample Size Considerations

This is an exploratory study and therefore no formal sample size calculations have been conducted. Sample size is primarily driven by feasibility and knowledge of disease heterogeneity to sufficiently evaluate the primary and supportive secondary objectives of the study.

Group A: Healthy Volunteers:

Approximately 4 to 12 subjects will be recruited. After approximately 4 subjects have been scanned, the variability in the imaging parameters will be assessed, after which up to 8 additional subjects may be recruited as following: a maximum of an additional 4 for ^{11}C-MET PET/CT plus MRI (total maximum of 8 subjects for ^{11}C-MET PET/CT), with the option for 4 extra for MRI only (total maximum of approximately 12 subjects for MRI).

Group B: Primary Sjögren's Syndrome Subjects

Approximately 8 to 12 pSS subjects will be recruited. Due to anticipated greater variability amongst patients, the variability of the imaging parameters will be assessed after approximately 8 subjects have been recruited, and consequently up to an additional 4 subjects may be recruited.

Following a literature review the following information was obtained for the imaging modalities of interest in the parotid glands in different populations. This historical information can be used in the variability assessment as outlined above.

Imaging modality; Parameter	Healthy Volunteers Mean [SD]	Patients (not pSS) Mean [SD] n	Patients (pSS) Mean [SD] n	Reference
^{18}F-FDG PET; SUV_{max}	n/a	1.80 [0.53] n=25	n/a	Basu, 2008
^{18}F-FDG PET; SUV_{max}	n/a	2.00 [not stated]	2.75 [0.61] n=32	Cohen, 2013
^{18}F-FDG PET; SUV	n/a	1.90 [0.68] n=78	n/a	Nakamoto, 2005
^{11}C-MET PET; SUV_{max}	6.00 [1.5] n=11	n/a	n/a	Isohashi 2013
DCE MRI, K_{trans}	0.20 [0.04] n=11	n/a	0.26 [0.05] n=21	Roberts, 2008

SD=Standard Deviation

Using estimates of parameter (this can be any parameter, SUV_{mean}, SUV, K_{trans}) variability, the precision of these estimates calculated as half width of a 95% confidence interval for the mean and expressed as distance from mean to limits, for 4, 8 and 12 subjects has been calculated (Table 5).

Table 5 Estimated Precision for the Mean of an Imaging Parameter

SD	Precision of Mean		
	N=4	N=8	N=12
0.05	0.08	0.04	0.03
0.5	0.80	0.42	0.32
1	1.59	0.84	0.64
1.5	2.39	1.25	0.95

For example, based upon the estimate of variability of 1 and a sample size of 12, it is estimated that the lower and upper bounds of the 95% confidence interval for the means of the imaging parameter (e.g. SUV_{mean}, SUV, K_{trans}) will be within approximately 0.62 of the point estimate.

9.2.1. Sample Size Sensitivity

No sample size sensitivity has been performed.

9.2.2. Sample Size Re-estimation or Adjustment

The variability of healthy volunteers will be assessed for the ^{11}C-MET PET/CT and multi-parametric MRI imaging modalities after approximately 4 healthy volunteers have been scanned, and with the aid of precision estimates for the observed variability outlined in Table 5, a recommendation may be made to increase the total healthy volunteers sample size to up to 8 (for both PET/CT and MRI). In this event, a further review of the multi-parametric MRI results may be performed after 8 healthy volunteers and a recommendation made to increase to a total of 12 for this imaging modality only. For feasibility reasons in the interests of limiting the exposure of healthy volunteers to radiation, a cap of 8 healthy volunteers is set for PET/CT.

Similarly the variability of pSS subjects will be assessed for the ^{11}C-MET PET/CT, ^{18}F-FDG PET/CT and multi-parametric MRI imaging modalities after approximately 8 pSS subjects have been scanned, and with the aid of precision estimates for the observed variability outlined in Table 5, a recommendation may be made to increase the total pSS subjects to 12.

For both groups, if sufficient data is collected for one or both PET/CT techniques, but not the other assessments (for example MRI), the additional subjects will only undergo the investigations needed (*eg* MRI and Visit 2 procedures without one or both PET/CT techniques), in order to minimize radiation exposure.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria
Safety	• Comprised of all subjects who receive/undergo any Visit 1 procedure.
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a radio-pharmacokinetic sample was obtained and analysed.

Additional analysis population(s) maybe defined in the Reporting and Analysis Plan (RAP).

9.3.2. Interim Analysis

No formal interim analysis will be performed, however a review of the imaging results will be performed for sample adjustment depending on the variability of the data as described in Section 9.2.2.

9.4. Key Elements of Analysis Plan

9.4.1. Primary analyses

Data for FDG PET/CT will be listed and summarized by quantitative parameter and Region of Interest (ROI). The data will be further explored graphically to examine:

- The parameter values across relevant ROI for each pSS subject
- The between-subject variability in parameter values by ROI
- Summary measures calculated across all relevant ROI (*eg*. maximum uptake, average uptake, total inflammatory volume, total number of lesions) and how these summary measures vary between patients.
- Asymmetry in parameter values between left and right parotid glands

Similar analyses may be performed for quantitative data from ^{11}C-MET PET/CT and multi-parametric MRI. For those imaging modalities, both HV and pSS are scanned, such that all displays will additionally denote group. An exploratory comparison of pSS vs HV may be performed for each quantitative parameter as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval. Further details are outlined in the reporting analysis plan (RAP).

9.4.2. Secondary Analyses

Descriptive statistics and/or graphical displays will be generated for all derived parameters from dynamic PET imaging and PK analyses. If data permits, statistical analyses of ^{11}C-MET PET radio-PK modelling indices with ^{11}C-MET static imaging matrices will be conducted to assess correlation.

9.4.3. Other/Exploratory Analyses

Details of the planned analyses for exploratory objectives to compare imaging parameters, explore their potential associations and the correlation of signals to clinical assessment measures and laboratory markers will be defined in the RAP.

Further details of proposed analyses will be specified 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 enrolment of subjects begins.

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

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 International Conference for Harmonisation (ICH) 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 favourable opinion/approval of the study protocol and amendments as applicable.
- Obtaining signed informed consent.
- Investigator reporting requirements (*eg* reporting of AEs/SAEs/protocol deviations to IRB/IEC).
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study.
- 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 CRF will serve as the source document.

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

- 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 multicentre 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 images in digital form will also be retained and may be used for future further analysis.

The records must be maintained to allow easy and timely retrieval, when needed (*eg* 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 (*eg* 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 Publically 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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Exploratory endpoints may be evaluated and reported outside the main Clinical Study Report.

11. REFERENCES

Affoo R, Foley N, Garrick R, Siqueria W and Martin R. Meta analysis of salivary flow rates in young and older adults.. Journal of the American Geriatrics Society. 2015: 63, p2142-2151.

Bakheet, S. M. and J. Powe . "Benign causes of 18-FDG uptake on whole body imaging." Semin Nucl Med 1998, 28(4): 352-358.

Basu, S., Houseni, M. and Alavi, A. Significance of incidental fluorodeoxyglucose uptake in the parotid glands and its impact on patient management. Nuclear Medicine Communications, 2008, 29(4), pp.367-373.

Buus, S., C. Grau, O. L. Munk, D. Bender, K. Jensen and S. Keiding. "^{11}C-MET PET, a novel method for measuring regional salivary gland function after radiotherapy of head and neck cancer." Radiother Oncol 2004, 73(3): 289-296.

Cohen, C., Mekinian, A., Uzunhan, Y., Fauchais, A., Dhote, R., Pop, G., Eder, V., Nunes, H., Brillet, P., Valeyre, D., Fain, O. and Soussan, M. 18F-fluorodeoxyglucose positron emission tomography/computer tomography as an objective tool for assessing disease activity in Sjögren's syndrome. Autoimmunity Reviews, 2013, 12(11), pp.1109-1114.

Deloar HM, Fujiwara T, Nakamura T, Itoh M, Imai D, Miyake M, Watanuki S. Estimation of internal absorbed dose of L-[methyl-^{11}C]methionine using whole-body positron emission tomography. Eur J Nucl Med. 1998 Jun;25(6):629-33. PMID

DOTAREM Summary of product characteristics (SPC) [http://www.mhra.gov.uk/spc-pil/?prodName=DOTAREM%20SOLUTION%20FOR%20INJECTION&subsName=GADOTERIC%20ACID&pageID=SecondLevel]

Fox, R. I. "Sjögren's syndrome." Lancet 2005, 366(9482): 321-331.

Glaudemans, A. W., R. H. Enting, M. A. Heesters, R. A. Dierckx, R. W. van Rheenen, A. M. Walenkamp and R. H. Slart. "Value of ^{11}C-MET PET in imaging brain tumours and metastases." Eur J Nucl Med Mol Imaging 2013, 40(4): 615-635.

Gomes Pde, S., G. Juodzbalys, M. H. Fernandes and Z. Guobis. "Diagnostic Approaches to Sjögren's syndrome: a Literature Review and Own Clinical Experience." J Oral Maxillofac Res 2012, 3(1): e3.

Harris, S. M., J. C. Davis, S. E. Snyder, E. R. Butch, A. L. Vavere, M. Kocak and B. L. Shulkin (2013). "Evaluation of the biodistribution of ^{11}C-MET in children and young adults." J Nucl Med 2013, 54(11): 1902-1908.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.].

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

Helmick, C. G., D. T. Felson, R. C. Lawrence, S. Gabriel, R. Hirsch, C. K. Kwoh, M. H. Liang, H. M. Kremers, M. D. Mayes, P. A. Merkel, S. R. Pillemer, J. D. Reveille, J. H. Stone and W. National Arthritis Data. "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I." Arthritis Rheum 2008, 58(1): 15-25.

Houweling, A. C., T. Schakel, C. A. van den Berg, M. E. Philippens, J. M. Roesink, C. H. Terhaard and C. P. Raaijmakers. "MRI to quantify early radiation-induced changes in the salivary glands." Radiother Oncol 2011, 100(3): 386-389.

ICRP. Pregnancy and Medical Radiation. ICRP Publication 2000, 84. Ann. ICRP 30 (1).

ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103, 2007. Ann. ICRP 37 (2-4).

Isohashi, K., Shimosegawa, E., Kato, H., Kanai, Y., Naka, S., Fujino, K., Watabe, H. and Hatazawa, J. Optimization of [^{11}C]-methionine PET study: appropriate scan timing and effect of plasma amino acid concentrations on the SUV. EJNMMI Research, 2013, 3(1), p.27.

Nakamoto, Y., Tatsumi, M., Hammoud, D., Cohade, C., Osman, M. and Wahl, R. (). Normal FDG Distribution Patterns in the Head and Neck: PET/CT Evaluation1. Radiology, 2005, 234(3), pp.879-885.

Roberts, C., Parker, G., Rose, C., Watson, Y., O'Connor, J., Stivaros, S., Jackson, A. and Rushton, V. Glandular Function in Sjögren Syndrome: Assessment with Dynamic Contrast-enhanced MR Imaging and Tracer Kinetic Modeling—Initial Experience 1. Radiology, 2008, 246(3), pp.845-853.

Seror R, Bootsma H, Saraux A, et al. Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis 2014; Dec 5. Pii: annrheumdis-2014-206008.

Su GY, Xu XQ, Wang YY, Hu H, Shen J, Hong XN, Shi HB, and Wu FO. Feasibility study of using intravoxel incoherent motion MRI to detect parotid gland abnormalities in early-stage Sjögren syndrome patients. J. Magn. Reson. Imaging, 2015. doi:10.1002/jmri.25096. PMID: 26583877

van der Aart J, Hallett WA, Rabiner EA, Passchier J, Comley. RA Radiation dose estimates for carbon-11-labelled PET tracers.. Nucl Med Biol. 2012 Feb;39(2):305-14. doi: 10.1016/j.nucmedbio.2011.08.005. Epub 2011 Oct 26. Review. PMID: 22033023

Vitali C., S. Bombardieri, R. Jonsson, H. M. Moutsopoulos, E. L. Alexander, S. E. Carsons, T. E. Daniels, P. C. Fox, R. I. Fox, S. S. Kassan, S. R. Pillemer, N. Talal, M. H. Weisman and S. European Study Group on Classification Criteria for Sjögren's .

"Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group." Ann Rheum Dis 2002, 61(6): 554-558.

World Health Organization. Report of a joint FAO/WHO/UNU expert consultation (WHO Technical Report Series 935). 2007, ISBN: 92 4 120935 6.

Ziakas, P. D., L. S. Poulou and L. Thanos. "Towards integrating positron emission tomography for work-up of patients with Sjogren's syndrome and associated lymphomas." Autoimmun Rev 2014, 13(3): 327-329.

12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ADC	Apparent Diffusion Coefficient
AE	Adverse Event
AECG	American European Consensus Group
ALT	Alanine Transaminase
Anti-SSa	Anti-Sjögren's-syndrome-related antigen A
ARSAC	Administration of Radioactive substances Advisory Committee
AST	Aspartate aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computed Tomography
CV%	Percentage Coefficient of Variation
D	Pure Diffusion Coefficient
DCE	Dynamic Contrast Enhanced
DW	Diffusion Weighted
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EU	European Union
EULAR	European League Against Rheumatism
f	Microvascular Volume Fraction
FAO	Food and Agriculture Organization of the United Nations
FDG	Fluorodeoxyglucose
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FT	Fourier Transform
GC	Gas chromatography
GCP	Good Clinical Practice
Gd	Gadolinium
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
HV	Healthy Volunteers
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immune Histochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRE	Initial Rate of Enhancement
IV	Intravenous
IVIM	Intravoxel Incoherent Motion
K_{trans}	Exchange Rate
M	Meter
MedDRA	Medical Dictionary for Regulatory Activities
ME	Maximal Signal Intensity Enhancement
MET	Methionine
MRI	Magnetic Resonance Imaging
MS	Mass Spectroscopy
mSv	Millisievert
NRS	Numeric Rating Scale
PET	Positron Emission Tomography
PK	Pharmacokinetic
pSS	Primary Sjögren's Syndrome
RAP	Reporting Analysis Plan
ROI	Region of Interest
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SPC	Summary of product characteristics
SRM	Study Reference Manual
SSb	anti Sjögren's syndrome type B
TIV	Total Inflammatory Volume
UK	United Kingdom
ULN	Upper Limit of Normal
UNU	United Nations University
WHO	World Health Organisation

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Dotarem

12.2. Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow up and Reporting of Adverse Events

12.2.1. 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms (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. • 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. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> 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.

12.2.2. 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:

c. Results in death

d. 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.

e. 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 fulfils 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.

f. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

g. Is a congenital anomaly/birth defect

h. Other situations:

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

i. Is associated with liver injury <u>and</u> impaired liver function defined as:

- Alanine Transaminase (ALT) ≥ 3x Upper Limit of Normal (ULN) and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and International Normalised Ratio (INR)** >1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** 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.

12.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure

- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.2.4. 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 Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire 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.

12.2.5. 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.

12.2.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- 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 the SAE coordinator.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- 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 the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined oestrogen and progestogen oral contraceptive [Hatcher, 2011])
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- 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 [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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.

12.3.2. Collection of Pregnancy Information

Female Subjects Enrolled on the Study

- 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 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.
- Any termination of pregnancy will be reported, regardless of foetal 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. 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.