Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	A Pilot Study to Evaluate Molecular Imaging Methods in Primary Sjögren's Syndrome
Compound Number	:	None
Effective Date	:	08-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 203818.
- This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe all planned analyses and outputs required for the final Clinical Study Report (CSR) of the study 203818.
Protocol	• This RAP is based on the protocol amendment 1 [(Dated: 24/MAY2017) of study 203818 (GSK Document No.: 2015N227551_01] and eCRF Version 1.
Primary Objective	• To investigate the use of ^{18}F-FDG PET/CT in assessing increased glucose uptake as a biomarker of inflammation in pSS subjects. • To investigate the use of ^{11}C- MET PET/CT in assessing salivary glandular function in pSS subjects and healthy volunteers. • To investigate the use of multi-parametric MRI in assessing salivary gland inflammation, function and structure in pSS subjects and healthy volunteers.
Primary Endpoint	• Semi-quantitative parameters of uptake in selected body areas, including salivary glands for ^{18}F-FDG: - Standardised Uptake Value (SUV). - Tissue-to-reference (T/R) ratio. - Total inflammatory volume (TIV) where anatomically relevant. • Semi-quantitative parameters of uptake in selected areas, including salivary glands for ^{11}C-MET: - SUV - T/R ratio - TIV where anatomically relevant. • 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.
Study Design	This is an imaging study using PET/CT and multi parametric MRI to investigate the potential to characterise and quantify disease manifestation in pSS subjects, not involving therapeutic intervention. A minimum of 4 and up to 12 healthy volunteers will be enrolled in Group A (up to 8 subjects for ^{11}C-MET PET/CT imaging, up to 12 for MRI) and 8 to 12 pSS subjects will be enrolled in Group B. • 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-

Overview	Key Elements of the RAP
	MET PET/CT (as for Group A) and ^{18}F-FDG PET/CT (head to hip).
Planned Analyses	• Interim analyses are detailed within Section 3.1 where applicable. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze of the study data.
Analysis Populations	• The Screened Population (Comprises of subjects who sign the Informed Consent) will be used for the evaluation of Screen Failure subjects • The Safety Population (Comprised of all subjects who receive/undergo any Visit 1 procedure). will be used for the evaluation of Study Population and Safety. • The Pharmacokinetic (PK) Population (Comprised of subjects in the 'Safety" population for whom radio-pharmacokinetic sample was obtained and analysed) will be used for the evaluation of Pharmacokinetic Analysis.
Hypothesis	• There are no formal hypotheses being tested in the study; instead an estimation and inference approach will be adopted to evaluate the objectives.
Primary Analyses	• Descriptive statistics and graphical displays, if appropriate, will be presented for all FDG PET/CT derived parameters across the regions of interest (ROI) for all pSS subjects and for all ^{11}C-MET PET/CT and 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 MRI derived quantitative parameter as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval.
Secondary Analyses	• Descriptive statistics and graphical displays, if appropriate, will also be presented 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.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol [(Dated: 24/MAY/2017)]. However, the following objective has been added as this was not included in the protocol:

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
• To assess the safety and tolerability of study procedures, including ^{18}F-FDG PET/CT (pSS only), ^{11}C- MET PET/CT, multiparametric MRI and salivary gland biopsy (pSS only).	• Safety and tolerability (Haematology, Clinical Chemistry, Vital Signs, Adverse Events)

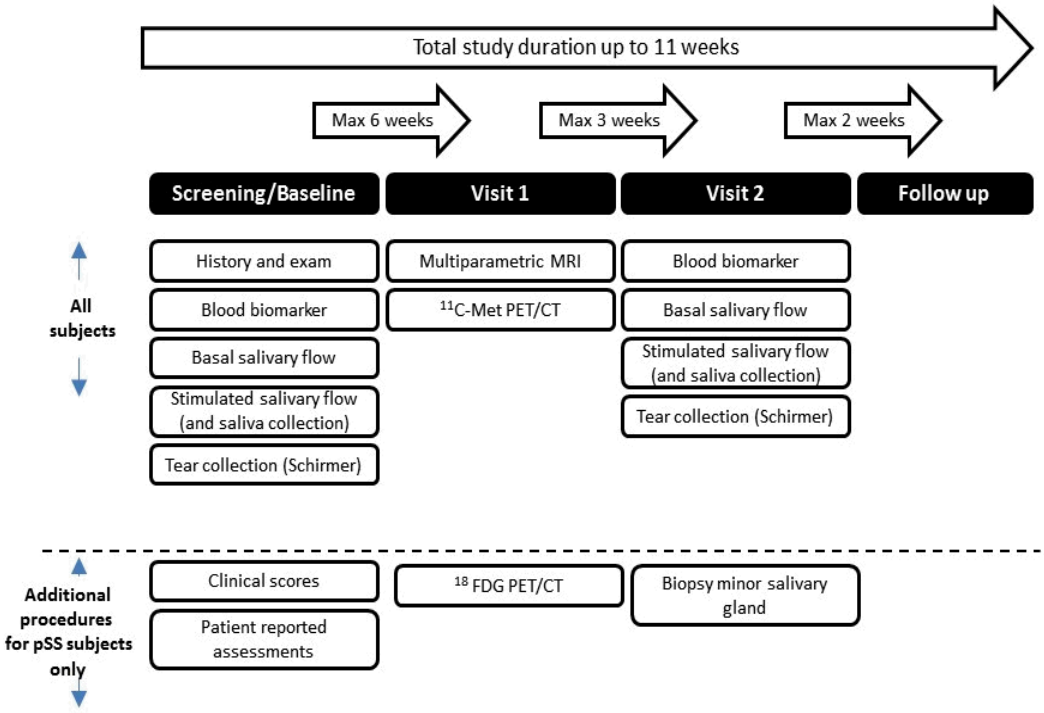
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• 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-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 : - Standardised Uptake Value (SUV) - Tissue-to-reference ratio - Total Inflammatory Volume (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 Objectives	**Secondary Objectives**
• 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

Objectives	Endpoints
	in ^{11}C-MET.
Exploratory Objectives	**Exploratory Objectives**
• 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 gland (systemic) abnormalities detected on ^{18}F-FDG PET/CT and ^{11}CMET 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	• 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

Objectives	Endpoints
subjects from healthy volunteers.	distinguishing pSS subjects from healthy volunteers. • Samples collected will be saliva, tears and plasma.
• To assess the safety and tolerability of study procedures, including ^{18}F-FDG PET/CT (pSS only), ^{11}C- MET PET/CT, multiparametric MRI and salivary gland biopsy (pSS only).	• Safety and tolerability (Haematology, Clinical Chemistry, Vital Signs, Adverse Events)

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	This is an imaging study using PET/CT and multi parametric MRI to investigate the potential to characterise and quantify disease manifestation in pSS subjects, not involving therapeutic intervention. • There will be 2 groups of subjects: Group A (healthy volunteers) and Group B (pSS subjects). Both groups will undergo a screening/baseline visit initially, during which, after informed consent, eligibility will be assessed and baseline assessments will be taken. This will include measurement of basal and stimulated salivary flow rate (and collection of saliva), a blood sample for biomarkers, a Schirmer's test and collection of exhaled breath (metabolomics). Detailed description can be found in the Time and Events table (Appendix 1: Time & Events). • Visit 1 is the imaging visit(s). The imaging visit(s) must occur within 6 weeks after the screening visit. Healthy volunteers (Group A) will undergo an MRI of the salivary glands and ^{11}C-MET PET/CT (dynamic scan of the salivary glands followed by half body, head to hip static scan). pSS subjects (Group B) will undergo MRI of the salivary glands, ^{11}C-MET PET/CT (as for Group A) and ^{18}F-FDG PET/CT (head to hip) (details in Time and

Overview of Study Design and Key Features	
	Events Table). • Visit 2 should 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), and blood samples for metabolomics/proteomics. 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.
Contrast	• ^{18}F-FDG (Group B only) radiotracer injected prior to PET/CT scanning. • ^{11}C-MET radiotracer injected prior to PET/CT scanning. • Gadoterate meglumine (Dotarem®) contrast agent administered prior to MRI scanning
Tracer Assignment	• All subjects will undergo MRI and ^{11}C-MET PET/CT at study visit 1. • pSS subjects (Group B) will also undergo ^{18}F-FDG PET/CT at study visit 1.

2.4. Statistical 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, however exploratory comparisons may be conducted as outlined below:

For ^{11}C-MET PET/CT and multi-parametric MRI, pSS subjects will be compared to healthy volunteers using an estimation approach, providing point estimates of differences (or ratios as applicable) with 95% confidence intervals.

Descriptive summary tables and graphical plots will be used to summarise all the imaging parameters, if data permits.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analysis will be performed. However, informal reviews of the imaging parameters will be performed to guide the decision to increase the sample size for one or more imaging modalities depending on the variability of the data, as described in the Interim Decision Document.

3.2. Sample Size Re-estimation or Adjustment

This is detailed in the Interim Decision Document.

3.3. Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprises of subjects who sign the Informed Consent	• Screen Failures
Safety	• Comprised of all subjects who receives/undergoes any procedure on or after visit 1.	• Study Population • Safety • PET/CT Parameters • Multiparametric-MRI Parameters • Biomarkers • Histological scores • ESSDAI/ESSPRI • Physician and patient global assessments, ocular and oral numerical rating scales • Tear flow • Salivary (basal and stimulated) flow
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a radio-pharmacokinetic sample was obtained and analysed.	• PET/CT radio-PK Concentrations • Dynamic ^{11}C-MET PET/CT metrics

NOTES:

- Please refer to Appendix 11: List of Data Displayswhich details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be listed.

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the listings of protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
General Considerations for Data Analyses & Data Handling Conventions	
11.1	Appendix 1: Time & Events
11.2	Appendix 2: Data Display Standards & Handling Conventions
11.3	Appendix 3: Derived and Transformed Data
11.4	Appendix 4: Premature Withdrawals & Handling of Missing Data
11.5	Appendix 5: Values of Potential Clinical Importance
11.6	Appendix 6: Multicentre Studies
11.7	Appendix 7: Examination of Covariates, Subgroups & Other Strata
11.8	Appendix 8: Multiple Comparisons & Multiplicity
11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
11.10	Appendix 10 – Abbreviations & Trade Marks
11.11	Appendix 11: List of Data Displays
11.12	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Safety population. Screen failures will be listed based on the "Screened" population.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated	
	Table	Listing
Subject Disposition		
Subject Disposition	Yes	
Reasons for Screen Failure		Yes
Subjects by Centre	Yes	
Reasons for Study Withdrawal		Yes
Protocol Deviations		
Important Protocol Deviations		Yes
Subjects with Inclusion/Exclusion Criteria Deviations		Yes [1]
Populations Analysed		
Study Populations and Exclusions	Yes	
Subjects Excluded from Any Population		Yes
Demographic and Baseline Characteristics		
Demographic Characteristics	Yes	Yes
Race and Racial Combinations	Yes	Yes [2]
History of Tobacco Use		Yes
Prior and Concomitant Medications		
Current and Past Medical Conditions		Yes
Concomitant Medications	Yes	Yes
Primary Sjogren's Syndrome History		Yes

NOTES:
[1] Listing also includes analysis population exclusions.
[2] Listing of race.

7. PRIMARY STATISTICAL ANALYSES

7.1. Imaging Analyses

7.1.1. Overview of Planned Imaging Analyses

The imaging analyses will be based on the Safety population, unless otherwise specified.

Table 3 provides an overview of the planned imaging analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Imaging Analyses

Endpoint / Parameter	Untransformed						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
^{18}F-FDG PET/CT semi-quantitative parameters							
$SUV_{(mean/max/peak)}$, T/R Ratio, TIV				Yes[1]	Yes[1]	Yes[1]	Yes[1]
^{11}C-MET PET/CT semi-quantitative parameters							
$SUV_{(mean/max/peak)}$, T/R Ratio, TIV	Yes[3]	Yes[3]		Yes[2]		Yes[2]	Yes[2]
Multiparametric MRI quantitative parameters							
K_{trans}[4], ADC[4], D[4] and f[4]	Yes[3]	Yes[3]		Yes[2]		Yes[2]	Yes[2]

NOTES:

- T = Table, F = Figure, L = Listing
- SUV = Standard Uptake Value, T/R Ratio = Tissue-to-reference ratio, TIV = Total Inflammatory Volume (TIV), K_{trans} = Exchange rate, ADC = Apparent Diffusion Coefficient, f = Microvascular volume fraction D = Pure Diffusion Coefficient
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1: By region of interest (ROI)
- 2: By region of interest (ROI) and group (Healthy Volunteers (HV) or primary Sjogren's Syndrome (pSS) patient).
- 3: If data permits. Stats analysis for $SUV_{mean/max/peak}$ for ^{11}C-MET PET/CT and K_{trans}, D and f for MRI.
- 4: Median and IQR (Interquartile Range) values for each parameter will be used.

7.1.1.1. ^{18}F-FDG PET/CT

Descriptive statistics will be calculated and presented graphically and in tabular format for ^{18}F-FDG semi-quantitative derived parameters including SUV, Tissue-to-reference ratio and TIV (as data permits). All parameters will be listed by ROI (where ROI will be sorted by relevance to pSS subjects and ordered as Parotid gland, lacrimal, submandibular and lastly any other gland in alphabetical order). When applicable for a given ROI, the outputs will be separated by the side of the ROI having higher parameter values and lower parameter values. Aggregated measures (left-right combined) will use measures extracted over the combined ROI's, rather than left-right averages to not introduce a bias towards the smaller gland.

The data may be further explored using scatter plots to examine asymmetry in parameter values between left and right parotid glands.

Further details are given in Appendix 11: List of Data Displays.

7.1.1.2. ^{11}C-MET PET/CT

Statistical analysis comparing the subject group (HV or pSS patient) will be conducted for ^{11}C-MET PET/CT parameters (including but not limited to SUV_{mean}, SUV_{max} and SUV_{peak}, as data permit), see Section 7.1.2 for detail.

Descriptive statistics will be calculated and presented graphically and in tabular format for ^{11}C-MET semi-quantitative derived parameters including SUV, Tissue-to-reference ratio and TIV and size of abnormality (as data permits). All parameters will be listed by group (HV or pSS patient) and ROI (where ROI will be sorted by relevance to pSS subjects and ordered as Parotid gland, lacrimal, submandibular and lastly any other gland in alphabetical order). When applicable for a given ROI, the analysis and summary outputs will be separated by the side of the ROI having higher parameter values and lower parameter values. Aggregated measures (left-right combined) will use measures extracted over the combined ROI's, rather than left-right averages to not introduce a bias towards the smaller gland.

The data may be further explored using scatter plots to examine asymmetry in parameter values between left and right parotid glands.

Further details are given in Appendix 11: List of Data Displays.

7.1.1.3. Multiparametric MRI

Statistical analysis comparing the subject group (HV or pSS patient) will be conducted for Multiparametric parameters (including but not limited to K_{trans}, D and f, as data permit), see Section 7.1.2 for detail. The median values of these parameters will be used for analysis.

Descriptive statistics will be calculated and presented graphically and in tabular format for multiparametric MRI quantitative derived parameters including but not limited to (median and IQR) K_{trans}, (median and IQR) ADC, (median and IQR) pure diffusion coefficient (D), and (median and IQR) microvascular fraction (f) as data permits. All parameters will be listed by group (HV or pSS patient) (and ROI, if data permits). When applicable for a given ROI, the analysis and summary outputs will be separated by the side of the ROI having higher parameter values and lower parameter values, as well as aggregated value. Aggregated measures (left-right combined) will use measures extracted over the combined ROI's, rather than left-right averages to not introduce a bias towards the smaller gland. As some of the MRI sequences may capture a reduced field-of-view of the salivary glands, the fraction of each gland that is analysed may be reported.

The data will be further explored using scatter plots and line plots to examine asymmetry in parameter values between left and right glands

Further details are given in Appendix 11: List of Data Displays.

7.1.1.4. Comparison of pSS subjects with HV

An exploratory comparison of pSS vs HV may be performed for ^{11}C-MET PET/CT and multiparametric MRI derived parameters as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval obtained from the analysis described in Section 7.1.2.

7.1.2. Planned Imaging Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• ^{11}C-MET PET/CT derived parameters, including but not limited to SUV_{peak}, SUV_{mean}, SUV_{max} • Multiparametric MRI derived parameters, including but not limited to (median and IQR) K_{trans}, (median and IQR) Pure diffusion coefficient (D), (median and IQR) microvascular volume fraction (f) and (median and IQR) ADC.
Model Specification
• Parameters will be statistically analysed individually using an Analysis of Variance (ANOVA) model. • Terms fitted in the ANOVA model will include: Fixed categorical : Subject group (HV or pSS patient)
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses : Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Estimates of Difference (pSS-HV) (or Ratio (pSS/HV) if $\log_e$ transformed) and 95% confidence interval for the derived parameters will be presented by ROI[1]. • Plots of means (difference or ratio) and 95% confidence interval from the model will be generated for each ROI. • P-values will not be presented as formal hypothesis is not being tested. The interpretation will be based on point estimates and its precision (95% CI).

NOTES :

- [1]: When applicable for a given ROI, the analysis will be separated by the side of the ROI having higher parameter values and lower parameter values, and aggregated over both sides.

7.1.3. Bayesian Analysis

In addition, a Bayesian approach to the exploratory comparison of pSS vs HV analysis of the ^{11}C-MET PET/CT and multi-parametric MRI parameters will be used. The objective of this analysis is to allow interpretable probability statements for the difference in two groups.

For the endpoints defined in Section 7.1.2, the uncertainty of the endpoint will be described with probability density function $p(\mu)$, say, where 'μ' represents the parameter. $P(\mu)$ represents our 'prior belief', since very little is known about the distribution of such parameters, normal function is assumed to be suitable for the data. This will have an unknown mean and known variance taken from the raw data (i.e $x_j \sim N(\mu_j, \sigma_j^2)$ where j is

the pSS patient group or the HV group). A weakly-informative (vague) conjugate Normal prior density function with mean zero and a large variance will be adopted for the group mean ($P(\mu)=N(0,100^2)$).

The endpoint from the study data will be used to gather evidence, which will be characterised via its likelihood function (derived from the relevant sampling distribution, $l(x|\mu)$, say, where 'x' stands for 'data' or in our case the parameter values).

This will lead to a Normal posterior density function for the endpoints of interest. Should the data not support a Normal likelihood function, alternative parametric forms, such as a log-Normal density, will be investigated.

Bayes' theorem will be applied to derive the posterior density function $p(\mu_j,x_j)$. PROC MCMC will be used for the analysis in SAS. The number of burn-in iterations will be at least 10,000 and the number of MCMC iterations, excluding the burn-in iterations will be at least 5000.

The posterior distribution for each endpoint will be summarised by region and group, including mean, median, SD, interquartile range and 95% credible interval based on highest posterior density (HPD) interval.

Samples from the posterior distribution for the group mean $p(\mu_i,x_i)$for the pSS patients and for the HV subjects will be used to determine the posterior distribution for the ratio and difference of group means (pSS patients to the HV subjects). The posterior distribution for the ratio and difference of group means will be summarised by region and endpoint. Plots for the mean and 95% credible interval for the posterior distribution of the group mean and the difference of group means will be presented for each endpoint and region. Samples from the posterior distribution of the ratio of group means will be used to determine the probability that the ratio of the endpoints in pSS patients to HV subjects exceed 1 for each endpoint and region. This will be repeated for other values to allow us to plot a graph of probability of exceeding a certain value, for ratios of 1, 1.5 and 2. The ratio will be given such that group expected to have lower uptake will be used at the reference (denominator).

7.2. Pharmacokinetic Analyses

7.2.1. Overview of Planned Radio-Pharmacokinetic Analyses

The radio-PK analyses will be based on the PK population, unless otherwise specified. Influx rate constant (Ki) will be used as the imaging metric for ^{11}C-MET dynamic scan.

Table 4 provides an overview of the planned Radio-PK analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Radio-Pharmacokinetic Analyses.

Endpoint / Parameter/ Display Type	Untransformed[1]				
	Stats Analysis		Summary	Individual	
	T	F	T	F	L
Radioactivity concentrations (whole blood and plasma)					
static ^{18}F-FDG PET/CT					Yes
^{11}C-MET PET/CT			Yes	Yes[2,3]	Yes
Radiopharmacokinetic parameters (^{11}C-MET)					
Influx rate constant (Ki)	Yes[3]	Yes[3]	Yes		Yes
Administration Volume					
Tracer and contrast					Yes
Meal Ingested					
Totality of Meal ingested					Yes

NOTES:

- T = Table, F = Figure, L = Listings
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1]: Log_e transform if necessary
- [2]: By subject group for ^{11}C-MET
- [3]: Correlation between radioPK parameter (Ki) vs ^{11}C-MET PET/CT $SUV_{peak/mean/max}$ by the side of the gland with most/least uptake in and ROI.

7.2.2. Radiopharmacokinetic Parameters

7.2.2.1. Deriving Radiopharmacokinetic Parameters

Derivation of the influx rate constant (Ki) is described in the PET data acquisition and analysis protocol and the derived endpoint will be received from Imanova.

7.2.2.2. Statistical Analysis of Radiopharmacokinetic Parameters

Tracer concentrations in whole blood and plasma will be summarized and listed by subject groups for static ^{18}F-FDG and ^{11}C-MET and Dynamic ^{11}C-MET. Individual, concentration-time curves will be plotted. The radio-pharmacokinetic parameter Influx Rate Constant (K_i) for ^{11}C-MET PET/CT will be summarized and listed by subject groups.

^{11}C-MET Influx rate constant (Ki) from dynamic ^{11}C-MET PET/CT scan will be graphically compared to ^{11}C-MET static scan $SUV_{peak/mean/max}$ or parameters derived by normalization with blood or other references, in the salivary gland region using a scatter plot by subject group. In addition to this, the correlation will be calculated and summarised between these parameters to compare static and dynamic imaging metrics.

8. SAFETY ANALYSES

8.1. Overview of Planned Adverse Events Analyses

The Safety analyses will be based on the Safety population, unless otherwise specified. Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute[1]	
	Summary Table	Individual Listing
Adverse Events (AEs)		
All AEs by SOC	Yes	Yes
Common AEs by Overall Frequency[2]	Yes	
Subjects & No. of Occurrences of Common Non-Serious AEs by SOC and PT[2]	Yes	
Subject Numbers for Individual AEs		Yes
Relationship Between AE SOCs, PT & Verbatim Text		Yes
Serious and Other Significant AEs		
Reasons for Considering as a Serious AE		Yes
AEs Leading to Withdrawal from Study by Overall Frequency	Yes	Yes
Subjects and Number of Occurrences of Serious and Fatal Serious AEs	Yes	

NOTES:

- SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1]: All outputs by subject group (HV and pSS)
- [2]: Common defined by ≥ 2 subjects

8.2. Overview of Planned Clinical Laboratory Analyses

The Clinical Laboratory analyses will be based on the "Safety" population, unless otherwise specified.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 6 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute
	Individual Listing
Chemistry	
Chemistry	Yes
Hematology	Yes
Urinalysis	Yes

Endpoint / Parameter/ Display Type	Absolute
	Individual
	Listing
Other Screening Tests	Yes
Vital Signs	
Vital Signs for Subjects with Values of Potential Clinical Importance (PCI)	Yes

NOTES:,

- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

9. OTHER STATISTICAL ANALYSES

9.1. Exploratory Analyses

9.1.1. Overview of Exploratory Analyses

The exploratory analyses will be based on the Safety population, unless otherwise specified.

Table 7 provides an overview of the planned exploratory analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 7 Overview of Planned Exploratory Analyses

Endpoint	Untransformed				
	Absolute				
	Summary		Individual		Stats Analysis
	T	F	F	L	T
Salivary gland					
Basal and Stimulated salivary flow	Yes		Yes	Yes	Yes[1]
Histological scores[2]	Yes		Yes	Yes	Yes[1]
Lacrimal Gland					
Schirmer's test	Yes		Yes	Yes	Yes[1]
Disease index[2]					
Disease activity measures[3]	Yes			Yes	
ESSDAI and ESSPRI			Yes		Yes[1]
ESSDAI component scores	Yes			Yes	
ESSPRI component scores				Yes	
Multiparametric MRI quantitative parameters[5]					
(median and IQR) IRE, (median and IQR) ME, (mean) Lipid Content, (median and IQR) T1 relaxation, (median and IQR) D* and (mean) gland volume	Yes[6]	Yes[6]		Yes[6]	Yes[1, 7]
Multiparametric MRI Questionnaire					
Dental History				Yes	
Sjogren's specific biomarkers[2]					
Laboratory biomarkers of disease activity[4]	Yes		Yes	Yes	Yes[1]

NOTES:

- T = Table, F = Figure, L = Listing, IQR = Interquartile Range, D* = Psuedo Diffusion
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- 1: Summary table for correlation.
- 2: pSS subjects only – more detail below
- 3: These include ESSDAI, ESSPRI, Patient Global Assessment, Physician Global Assessment, Oral dryness

numerical rating, ocular dryness numerical rating

- 4: This may include metabolomic and proteomic profiles if applicable and also include data from healthy subjects. See Section 11.3.6 for more details.
- 5: If data permits.
- 6: By region of interest (ROI) and group (HV or pSS patient).
- 7: Summary table of comparison between HV and pSS group.

Descriptive statistics (Mean, Median, Standard Deviation, Minimum, Maximum) of absolute values of basal, stimulated salivary flow rate and score from Schirmer's test will be provided. The absolute values will be listed by subject groups.

The histological scores (see Section 11.3.5) and the various disease indices (see Section 11.3.4) – ESSDAI, ESSPRI, Patient and Physician global assessment of disease activity, oral and ocular dryness scales will be descriptively summarized and listed for pSS group only.

Descriptive statistics will be calculated for the exploratory multiparametric MRI quantitative derived parameters listed in Table 7 (as data permits) and presented in tables. All parameters will be listed by group (and ROI, as data permits). Mean (± SE bars) will be plotted for each parameter by ROI (if appropriate with panel for each side).

Correlation between ^{18}F-FDG PET/CT (pSS subjects only), ^{11}C-MET PET/CT and MRI parameters (HV and pSS subjects) in the region of the salivary glands (parotid gland) will be explored using scatter plots. Plots will be in panel for each side (most vs least uptake) of the region scanned. The parameters will include, SUV_{peak} for PET/CT and K_{trans}, D and f for multiparametric MRI.

Furthermore, correlation between the imaging parameters mentioned above and

- histological scores (mean and maximum lymphoid organisation score and volume fraction) from the minor salivary gland biopsy
- Salivary flow rate – mean (from baseline and visit 2) stimulated and basal salivary flow rate, and mean difference (stimulated – basal)
- Measures of Disease Activity – ESSDAI and ESSPRI scores
- Lab biomarkers of disease activity – C3 and C4 levels
- Schirmer's test – length of paper wetted by eyes (panel for each side; least and most) and time to completely wet the strip (panel for each side; least and most).

may be explored using scatter plots (panel for each side) and statistical analysis summarised in tables. In addition, SUV_{peak} from the ^{11}C-MET PET/CT will be correlated with the ratio of IgG/IgA using scatter plots and summary tables of the correlation. See below for summary of correlations:

Method		11C-MET PET/CT	18F-FDG PET/CT	Multiparametric MRI
	Parameter(s)/Endpoint	SUVpeak	SUVpeak	(median) Ktrans, (median) D, (median) ADC, (median) f, (median) IRE, (median) ME, (mean) Lipid Content, (median) D* (pseudo diffusion), (mean) gland volume
11C-MET PET/CT	SUVpeak		Yes	
18F-FDG PET/CT	SUVpeak	Yes		
Multiparametric MRI	(mean) lipid content	Yes	Yes	Yes[1]
Histological scores	Max lymphocyte focus score	Yes	Yes	Yes
	Mean lymphocyte focus score			
	Max Lymphoid organisation grading			
	Mean Lymphoid organisation grading			
Salivary flow rate	Mean stimulated	Yes	Yes	Yes
	Mean basal			
	Mean difference			
Disease Activity	ESSDAI	Yes	Yes	Yes
	ESSPRI			
Lab biomarkers of disease activity	C3	Yes	Yes	Yes
	C4			
	IgG/IgA	Yes	Yes	Yes
Schirmer's test	Length wet per minute	Yes	Yes	

[1]: Correlation of lipid content with (median) Ktrans, IRE, ME, D, f, ADC.

If metabolomic and/or proteomic data is available in the study, these may be reported as a separate reporting effort in addition to the final SAC reporting effort. This will not contribute to the CPSR.

9.1.1.1. Comparison of pSS subjects with HV

An exploratory comparison of pSS vs HV may be performed for multiparametric MRI derived exploratory parameters as data permit, to estimate a difference (or ratio if log transformation is needed) with 95% confidence interval obtained from the analysis described in Section 9.1.2.

9.1.2. Planned Imaging Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Multiparametric MRI derived parameters; (median and IQR) IRE, (median and IQR) ME, (mean) Lipid Content, (median and IQR) T1 relaxation, (median and IQR) D* (pseudo diffusion) and (mean) gland volume
Model Specification
• Parameters will be statistically analysed using an Analysis of Variance (ANOVA) model. • Terms fitted in the ANOVA model will include: Fixed categorical : Subject group (HV or pSS patient)
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses : Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Estimates of Difference (pSS-HV) (or Ratio (pSS/HV) if $\log_e$ transformed) and 95% confidence interval for the derived parameters will be presented by ROI[1]. • Plots of means (difference or ratio) and 95% confidence interval from the model will be generated for each ROI. • P-values will not be presented as formal hypothesis is not being tested. The interpretation will be based on point estimates and its precision (95% CI).

NOTES : [1]: When applicable for a given ROI, the analysis will be separated by the side of the ROI having higher parameter values and lower parameter values, and aggregated over both sides.

10. REFERENCES

Cho, H., Yoo, J., Yun, C., Kang, E., Lee, H., Hyon, J., Song, Y. and Lee, Y. (2013). The EULAR Sjogren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjogren's syndrome patients: in comparison with non-Sjogren's syndrome patients. *Rheumatology*, 52(12), pp.2208-2217

GlaxoSmithKline Document Number 2015N227551_01 Study ID 203818: A Pilot Study to Evaluate Molecular Imaging Methods in Primary Sjögren's Syndrome. 24-MAY-2018

Interim Decision Document
https://biodocumentum.bio.corpnet1.com/webtoppr/drl/objectId/090f45f68622127b (00_No Asset-203818 Statistical Analysis Plan (Interim Decision Document) Version 001 (14-Sep-2017))

11. APPENDICES

Section	Appendix
General Considerations for Data Analyses & Data Handling Conventions	
Section 11.1	Appendix 1: Time & Events
Section 11.2	Appendix 2: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.3	Appendix 3: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 11.4	Appendix 4: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.5	Appendix 5: Values of Potential Clinical Importance
Section 11.6	Appendix 6: Multicentre Studies
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Section 11.8	Appendix 8: Multiple Comparisons & Multiplicity
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Other RAP Appendices	
Section 11.10	Appendix 10 – Abbreviations & Trade Marks
Section 11.11	Appendix 11: List of Data Displays
Section 11.12	Appendix 12: Example Mock Shells for Data Displays

11.1. Appendix 1 : Time & Events

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 [	X	
Blood biomarkers for ESSDAI	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.

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

11.2. Appendix 2: Data Display Standards & Handling Conventions

11.2.1. Study Treatment Display Descriptors

No study treatment is administered in this study. Subject group displays will be described as follows:

Subject Group Descriptions			
Dataset Display		Data Displays for Reporting	
Code	Description	Description	Order [1]
H	Healthy Volunteer	Healthy Volunteer	1
P	pSS Patient	pSS Patient	2

NOTES:

1. Order represents subject groups being presented in TFL, as appropriate.

11.2.2. Baseline Definition & Derivations

11.2.2.1. Baseline Definitions

For all endpoints, baseline will be taken as the value at the screening/baseline except for urine pregnancy test which is taken at baseline 2 (within 4-7 days prior to Visit 1).

11.2.2.2. Derivations and Handling of Missing Baseline Data

No change from baseline calculations are to be conducted. However, if required then the following derivation is to be used:

	Reporting Details
Change from Baseline	= Post-Baseline Visit Value – Baseline Value

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 11.2.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

11.2.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /ARPROD/NOCOMPOUND/MID203818/FINAL

Reporting Process	
QC Spreadsheet	: /ARWORK/NOCOMPOUND/MID203818/FINAL/DOCUMENTS

Analysis Datasets

- Analysis datasets will be created according to Integrated Data Standards Library (IDSL) GSK A&R dataset standards.

Generation of RTF Files

- RTF files will be generated for the final analysis tables and listings only.

Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  - 4.03 to 4.23: General Principles
  - 5.01 to 5.08: Principles Related to Data Listings
  - 6.01 to 6.11: Principles Related to Summary Tables
  - 7.01 to 7.13: Principles Related to Graphics

Formats

- All data will be reported according to the actual treatment the subject received unless otherwise stated.
- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected.
- Numeric data will be reported at the precision collected on the eCRF.
- The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - For Imaging related outputs, the planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, where the output is radio-pharmacokinetic related. For any other outputs the planned time relative to visit 1.
  - The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- Reporting for Data Listings:
  - For Imaging related outputs, planned and actual time relative to study contrast administration will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). For any other outputs, planned and actual time relative to Visit 1 will be shown in listings.
  - Unscheduled or unplanned readings will be presented within the subject's listings.
  - Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.

Unscheduled Visits

- Unscheduled visits will not be included in summary tables.
- Unscheduled visits will not be included in figures.
- All unscheduled visits will be included in listings.

Reporting Standards	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.3. Appendix 3: Derived and Transformed Data

11.3.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.
Study Day

• Calculated as the number of days from Visit 1 date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Visit 1 Date → Study Day = Ref Date – Visit 1 Date
  • Ref Data ≥ Visit 1 Date → Study Day = Ref Date – (Visit 1 Date) + 1

11.3.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • The reference day for age calculation will be screening visit.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$]

11.3.3. Imaging

Imaging Parameters
All imaging parameters datasets will contain ROI which will include the side of the ROI where applicable. A variable will be derived for the side with the higher (named 'High') and lower (named 'Low') parameter value. When ROI does not have a side or in the case where the sides have equal parameter values the variable will be 'NA'. The variable can be called 'Side', to aid with the reporting of the study. For MRI parameters, the aggregated score will be included for listing and summary tables and plots. No derivations will be conducted by GSK.

11.3.4. Disease Activity Index

Disease Activity Index

ESSDAI

The European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) is a systemic disease activity index that was designed to measure disease activity in patients with primary SS. The ESSDAI is a disease activity index that was generated in 2009, by consensus of a large group of worldwide experts from European and North American countries. The ESSDAI is a systemic diease activity index and includes 12 domains (i.e., organ systems; cutaneous, respiratory, renal, articular, muscular, peripheral nervous system (PNS), central nervous system (CNS), haematological, glandular, constitutional, lymphadenopathic, biological). Each domain is divided in three to four levels depending on their degree activity. The final score, the sum of all domain scores (given below), falls between 0 and theoretically 123, with 0 being no disease activity and 123 being most severe disease activity.

Domain	Activity level	Description
Constitutional - Exclusion of fever of infectious origin and voluntary weight loss	No=0	Absence of the following symptoms
	Low=3	Mild or intermittent fever (37.5°–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate=6	Severe fever (>38.5°C) / night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy - Exclusion of infection	No=0	Absence of the following features
	Low=4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate=8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High=12	Current malignant B-cell proliferative disorder*
Glandular - Exclusion of stone or infection	No=0	Absence of glandular swelling
	Low=2	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling
	Moderate=4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling

Disease Activity Index		
Articular - Exclusion of osteoarthritis	No=0	Absence of currently active articular involvement
	Low=2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate=4	1–5 (of 28 total count) synovitis
	High=6	≥6 (of 28 total count) synovitis
Cutaneous - Rate as 'No activity' stable long-lasting features related to damage	No=0	Absence of currently active cutaneous involvement
	Low=3	Erythema multiforma
	Moderate=6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High=9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary - Rate as 'No activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc.)	No=0	Absence of currently active pulmonary involvement
	Low=5	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test.
	Moderate=10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70%>DL_{CO}≥ 40% or 80%>FVC≥60%
	High=15	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL_{CO} < 40% or FVC<60%

Disease Activity Index		
Renal - Rate as 'No activity' stable long-lasting features related to damage, and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first	No=0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low=5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 mL/min)
	Moderate=10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High=15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
Muscular - Exclusion of weakness due to corticosteroids	No=0	Absence of currently active muscular involvement
	Low=6	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N)
	Moderate=12	Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N <CK ≤4N),
	High=18	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)

Disease Activity Index			
PNS - Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease	No=0	Absence of currently active PNS involvement	
	Low=5	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia	
	Moderate=10	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5or mild ataxia),	
		Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)	
	High=15	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia	
CNS - Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease	No=0	Absence of currently active CNS involvement	
	Moderate=10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment	

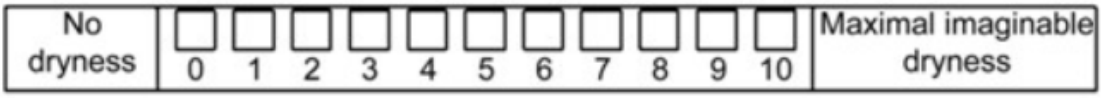
Disease Activity Index			
	High=15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.	
Haematological - For anaemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	No=0	Absence of autoimmune cytopenia	
	Low=2	Cytopenia of autoimmune origin with neutropenia (1000<neutrophils<1500/mm^3), and/or anaemia (10<haemoglobin<12 g/dL), and/or thrombocytopenia (100 000<platelets<150 000/mm^3) Or lymphopenia (500<lymphocytes<1000/mm3)	
	Moderate=4	Cytopenia of autoimmune origin with neutropenia (500≤neutrophils≤1000/mm^3), and/or anaemia (8≤haemoglobin≤10 g/dL), and/or thrombocytopenia (50 000≤platelets≤100 000/mm^3) Or lymphopenia (≤500/mm3)	
	High=6	Cytopenia of autoimmune origin with neutropenia (neutrophils <500/mm^3), and/or or anaemia (haemoglobin <8 g/dL) and/or thrombocytopenia (platelets <50 000/mm^3)	
Biological	No=0	Absence of any of the following biological features	
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L	
	Moderate=2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)	

Disease Activity Index

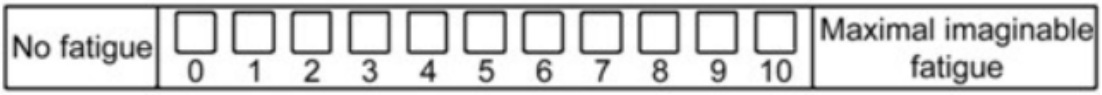
ESSPRI

The EULAR Sjögren's syndrome patient reported index (ESSPRI) was developed as a simple index for measuring pSS patient's symptoms. The ESSPRI is calculated by averaging the scales for pain, fatigue and dryness (Cho et al., 2013). The final ESSPRI score is therefore continuous and ranges from 0 to 10 with 10 being maximal pSS symptoms.

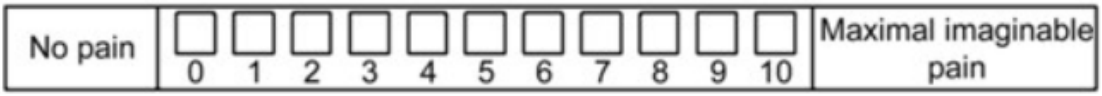
1) How severe has your dryness been during the last 2 weeks ?



2) How severe has your fatigue been during the last 2 weeks ?



3) How severe has your pain (joint or muscular pains in your arms or legs) been during the last 2 weeks ?



Seror R et al. Ann Rheum Dis doi:10.1136/annrheumdis-2013-204615

11.3.5. Histology

Histology

Two types of histology analysis will be conducted:

1. H&E
2. Immune Histochemistry (IHC)

Each analysis will be performed by two operators (blinded to the outcome of other's assessments). Average values will be calculated and reported.

The following parameters will be collected:

- Focus Score
- Volume Fraction

} H&E

- CD3/CD20 (T cell / B cell; double staining)
- CD21 (Germinal Centres)
- CD138 (plasma cells)
- IgG (B cell activity)
- IgM (B cell activity)
- IgA (B cell activity)
- Ki67 (proliferation)

} Immune Histochemistry (IHC)

Volume fraction = aggregate area / total glandular area

11.3.6. Laboratory Biomarkers of Disease Activity

Laboratory Biomarkers of Disease Activity

Laboratory Biomarkers of Disease Activity include (LBTESTCD):

- Serum bicarbonate (LBTESTCD=HC03_PLC)
- Serum chloride (LBTESTCD=CL_PLC)
- Cryoglobulin (LBTESTCD=CYRO_PLG)
- Urinary Protein creatinine radio (PRTCRT_URQ)
- Total Immunoglobulin (LBTESTCD=IG-PLC)
- IgG (LBTESTCD=IGG_PLC)
- IgA (LBTESTCD=IGA_PLC)
- IgM (LBTESTCD=IGM_PLC)
- Serum Monoclonal Protein – Electrophoresis (LBTESTCD=MPROTE_PLC)
- Complement component 3 (LBTESTCD=C3_PLC)
- Complement component 4 (LBTESTCD=C4_PLC)

- Anti-Sjogrens-syndrome-related antigen A (qualitative) (LBTESTCD=SJSSAA_PLG)
- Anti-Sjogrens-syndrome-related antigen B (qualitative) (LBTESTCD=SJSSAB_PLG)
- Serum creatinine (LBTESTCD=CRT_PLC)
- Urea/BUN (LBTESTCD=UREA_PLC)
- Glomerular filtration rate (MDRD)
- Creatine kinase (LBTESTCD=CK_PLC)
- Haemoglobin (LBTESTCD=HB_PLC)
- White blood cell count (LBTESTCD=WBC_PLC)
- Neutrophil count (LBTESTCD=NEUT_BLC)
- Lymphocyte count (LBTESTCD=LYMPH_BLC)
- Platelet count (LBTESTCD=PLT_PLC)

In addition to this, the ratio IgG/IgA will be derived and added to the list of labtest in the Analysis and Reporting dataset. The LBTESTCD will be IGG_IGA_RATIO and the derivation will simply be IgG ÷ IgA. If either value is missing or lower than LLQ then this ratio will be set to missing.

11.3.7. Salivary Flow Rate

Salivary Flow Rate

Salivary flow rate is measured at basal and stimulated state at screening/baseline and at follow-up.

Mean of baseline and follow-up visit will be calculated separately for stimulated and basal salivary flow rate. The mean will be calculated as:

- Mean Stimulated/Basal salivary flow = (Stimulated/Basal salivary flow at baseline + Stimulated/Basal salivary flow at follow-up) ÷ 2.

If value is missing at one time point (e.g. baseline), then the rate from the other time (follow-up) will be used for the mean.

The difference of the stimulate and basal salivary flow rate will be calculated for each time point:

- Screening/baseline difference = Stimulated salivary flow rate at baseline - Basal salivary flow rate at baseline
- Follow-up difference = Stimulated salivary flow rate at follow-up – Basal salivary flow rate at follow-up.

If one of the rate (stimulated or basal) is missing at one time point (e.g. baseline), then the rate

from the other time (follow-up) will be used to calculate the difference. If the measure of the rate is missing at both time points, then difference will be set to missing.

The mean of difference (stimulated-basal) will be derived as follows:

- Mean difference (stimulated – basal) salivary flow = (Screening/baseline difference + Follow-up difference) ÷ 2

11.3.8. Lacrimal Function

Lacrimal Function
The lacrimal function will be assessed using Schirmer's test. The Schirmer's test is to be performed at Baseline/Screening and Visit 2. At each time point, i) the amount of wetting of strip measured in millimetre scale, in 5 minutes ii) the time taken to complete saturation of the strip. The ratio of strip wetted to time (i/ii) will give mm of paper wetter per minute. Strip wet per minute = (mm of paper wet/time in seconds) x 60 The time will be given in minute seconds format and will be transformed to seconds. This value will be summarised and to correlate with imaging parameters. If one of the values (i or ii) is missing at one timepoint then the same value from the other time point will be used to calculate the ratio for a specific eye. If the measure of the rate is missing at both time points, then ratio will be set to missing.

11.4. Appendix 4: Premature Withdrawals & Handling of Missing Data

11.4.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who completed all phases of the study including the follow up. • Withdrawn subjects may be replaced in the study at the discretion of the sponsor. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.4.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.4.2.1. Handling of Missing Dates

Completely missing start or end dates will remain missing, with no imputation applied.

11.4.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	o Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. Unless this is after the end date of study; in this case the end of study date will be used. o The recorded partial date will be displayed in listings.
Adverse Events	o Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made:

Element	Reporting Detail
	○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if these results in a date prior to Visit 1 and the event could possibly have occurred during study from the partial information, then the Visit 1 date will be assumed to be the start date. ○ The AE will then be considered to start on-study (worse case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. Unless this is after the end date of study; in this case the end of study date will be used. ○ The recorded partial date will be displayed in listings.

11.4.2.3. Handling of Missing Data for Statistical Analysis

Missing data will remain missing with no imputation applied for the purposes of statistical analysis.

11.5. Appendix 5: Values of Potential Clinical Importance

11.5.1. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

11.5.2. Laboratory Values

Haematology				
Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
Albumin	G/L		30	
Calcium	mmol/L		2	2.75
Creatinine	umol/L			1.3 X ULN
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

11.6. Appendix 6: Multicentre Studies

A summary table for subject disposition will be displayed by centre, no other outputs will be produced by centre or highlighting the recruitment by site.

11.7. Appendix 7: Examination of Covariates, Subgroups & Other Strata

All the reporting will be separated by subject group, i.e. by healthy volunteers and pSS subjects. Subject group would be fitted as a fixed categorical variable in the ANOVA model described in Section 7.1.1.4.

11.8. Appendix 8: Multiple Comparisons & Multiplicity

No adjustments for multiplicity will be required.

11.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

11.9.1. Statistical Analysis Assumptions

Endpoint(s)	• ^{11}C-MET PET/CT parameters including but not limited to SUV_{peak}, SUV_{max} and $SUV_{mean.}$ • Multiparametric MRI parameters including but not limited to diffusivity (D), microvascular volume fraction (f) and K_{trans}. • Additional quantitative parameters, if deemed appropriate.
Analysis	• Analysis of Variance (ANOVA)
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data. Mann-Whitney U test will also be used when untransformed data cannot be assumed to be normal.	
Endpoint(s)	• Correlation between imaging parameters with o other imaging parameters o salivary and tear flow o histological scores o disease activity o lab biomarkers of disease activity
Analysis	• Pearson Correlation Coefficient
• Both variables should be normally distributed • Linear relationship between each of the two variables • Homoscedasticity of the data – equally distributed about the regression line. • Alternative, non-parametric method such as Spearman rank correlation will also be reported if assumptions are violated.	

11.10. Appendix 10 – Abbreviations & Trade Marks

11.10.1. Abbreviations

Abbreviation	Description
ADC	Apparent Diffusion Coefficient
AE	Adverse Event
ANOVA	Analysis of Variance
Anti-SSA/B	Anti-Sjögren's-syndrome-related antigen A/B
A&R	Analysis and Reporting
CI	Confidence Interval
CSR	Clinical Study Report
CT	Computed Tomography
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
D	Pure Diffusion Coefficient
D*	Pseudo Diffusion Coefficient
DOB	Date of Birth
DCE	Dynamic Contrast Enhanced
DP	Decimal Places
DW	Diffusion Weighted
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European League Against Rheumatism
f	Micro vascular volume fraction
FDG	Fluorodeoxyglucose
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
HV	Healthy Volunteers
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IHC	Immune Histochemistry
IP	Investigational Product
IRE	Initial Rate of Enhancement
IV	Intravenous
K_{trans}	Exchange Rate
ME	Maximal Enhancement
MET	Methionine
MRI	Magnetic Resonance Imaging
mSv	Millisievert
NRS	Numeric Rating Scale
PCI	Potential Clinical Importance
PD	Pharmacodynamic

Abbreviation	Description
PDMP	Protocol Deviation Management Plan
PET	Positron Emission Tomography
PK	Pharmacokinetic
pSS	Primary Sjögren's Syndrome
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
ROI	Region of Interest
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operation Procedure
SUV	Standardised uptake value
TFL	Tables, Figures & Listings
TIV	Total Inflammatory Volume
GSK	GlaxoSmithKline

11.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

11.11. Appendix 11: List of Data Displays

11.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.6	NA
Pharmacodynamic	2.1 to 2.9	2.1 to 2.13
Pharmacokinetic	3.1 to 3.3	3.1 to 3.2
Safety	4.1 to 4.5	NA
Biomarker	5.1 to 5.11	5.1 to 5.9
Section	**Listings**	
ICH Listings	1 to 21	
Other Listings	22 to 47	

11.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	NA	POP_Tn	POP_Ln
Pharmacodynamic	EFF_Fn	EFF_Tn	EFF_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Biomarker	PD_Fn	PD_Tn	PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.11.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
SAC	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

11.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition		SAC
1.2.	Safety	NS1	Summary of Number of Subjects by Centre ID		SAC
Populations Analysed					
1.3.	Screened	SP1	Summary of Study Populations		SAC
Demography					
1.4.	Safety	DM1	Summary of Demographic Characteristics for all Enrolled Subjects	Include summary of disease duration for pSS patients.	SAC
1.5.	Safety	DM1	Summary of Demographic Characteristics for Subjects Undergone a Scan	Include summary of disease duration for pSS patients. Exclude subjects who have not completed at least one scan.	SAC
1.6.	Safety	DM6	Summary of Race and Racial Combination		SAC
Concomitant Medications and Medical Conditions					
1.7.	Safety	CM1	Summary of Concomitant Medications		SAC

11.11.5. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
^{18}F-FDG PET/CT semi-quantitative parameters					
2.1.	Safety	EFF_T1	Summary of ^{18}F-FDG PET/CT parameters	Paginate by Parameter. Subheading 'Parameter: [name]'	SAC
^{11}C-MET PET/CT semi-quantitative parameters					
2.2.	Safety	EFF_T1	Summary of ^{11}C-MET PET/CT parameters	Paginate by Subject group and Parameters. To include ROI, side and SE with all other summary statistics. Subheading: 'Parameter: [name]' 'Subject Group: [name]'	SAC
2.3.	Safety	EFF_T4	Point Estimate and 95% CI for ^{11}C-MET PET/CT Derived Parameters of Difference in pSS vs. HV	Analysed by Parameter (SUVmean/SUVmax/SUVpeak) and ROI. When applicable for a given ROI, the analysis will be separated by the side. Summarize Means and Differences (or Ratios) with 95% CI.	SAC

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	Safety	EFF_T5	Summary of the Posterior Distribution of the Ratio and Difference of Group Means for ^{11}C-MET PET/CT Parameter by Region	Paginate by parameter and subject group. Parameters to include: SUVpeak, SUVmax and SUVmean. First two columns for ROI and side.	SAC
2.5.	Safety	EFF_T6	Posterior Probability that the Ratio and Difference of Group Means for ^{11}C-MET PET/CT Parameter Exceeds a Certain Value, by Region	Paginate by parameter and subject group. Parameters to include: SUVpeak, SUVmax and SUVmean. First two columns for ROI and side. Ratios of interest: 1, 1.5 and 2 Difference of interest: 0 Footnote: Ratio=HV/pSS Note: Values/inequality subject to change based on data	SAC

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Multiparametric MRI quantitative parameters					
2.6.	Safety	EFF_T1	Summary of Multiparametric MRI.	Paginate by Subject group and Parameters include (median and IQR) Ktrans, D, D*, f, ADC, IRE, ME,and (Mean) lipid content and gland volume as data permits. To include ROI, side (low/high/aggregated), and SE with all other summary statistics. Parameters to include:	SAC
2.7.	Safety	EFF_T4	Point estimate and 95% CI for Multiparametric MRI Derived Parameter of Difference in pSS vs. HV	Analysed by Parameter and Region of Interest. When applicable for a given ROI, the analysis will be separated by the side of the ROI. Parameters include (median and IQR) Ktrans, D, D*, f, ADC, IRE, ME,and (Mean) lipid content and gland volume as data permits. Summarize Means and Differences (or Ratios) with 95% CI. Note: P value not included as this is not a statistically powered study	SAC

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	Safety	EFF_T5	Summary of the Posterior Distribution of the Ratio and Difference of Group Means for Multiparametric MRI Parameter by Region	Paginate by parameter and subject group. Parameters to include but not limited to: Ktrans, ADC, D, and f. For each median values will be analysed. First two columns for ROI and side.	SAC
2.9.	Safety	EFF_T6	Posterior Probability that the Ratio and Difference of Group Means for Multiparametric MRI Parameter Exceeds a Certain Value, by Region	Paginate by parameter and subject group. Parameters to include but not limited to: Ktrans, ADC, D, f and volume. For each median values will be analysed. First two columns for ROI and side. Ratios of interest: 1, 1.5 and 2 Difference of interest: 0 Footnote: Ratio=HV/pSS Note: Values/inequality subject to change based on data	SAC

Note: The above summaries will be generated if data is available.

11.11.6. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
^{18}F-FDG PET/CT semi-quantitative parameters					
2.1.	Safety	EEF_F1	Plot of Individual ^{18}F-FDG PET/CT Parameters by ROI	Paginated by Parameter and ROI. Column panel by side. Plot Subject number along X axis and parameter value along Y axis.	SAC
2.2.	Safety	EFF_F2	Mean (+/- SE) of ^{18}F-FDG PET/CT Parameters	Paginated by Parameters and ROI. Plot Sides along X axis and Mean along Y axis. Note: If transformation is required then use median +/- IQR	
2.3.	Safety	EFF_F2	Mean (+/- 95% CI) of ^{18}F-FDG PET/CT Parameters	Paginated by Parameters and ROI. Plot Side along X axis and Mean along Y axis. Note: If transformation is required then use median +/- IQR	SAC
2.4.	Safety	EFF_F7	Ratio of SUV_{peak} (Left/Right) Assessing Asymmetry in ^{18}F-FDG PET/CT Parameter	X-axis: Subject Y-axis: Ratio of SUVpeak(left/right) Include reference line at Y=1. Footnote: Ratio of 1 (reference line) represents complete symmetry.	SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
^{11}C-MET PET/CT semi-quantitative parameters					
2.5.	Safety	EFF_F1	Plot of Individual ^{11}C-MET PET/CT Parameters by ROI	Paginated by Parameter and ROI. Column panel by side. Plot Subjects along X axis and parameter value along Y axis. Colour and symbol by subject group.	SAC
2.6.	Safety	EFF_F3	Mean (+/- SE) of ^{11}C-MET PET/CT Parameters.	Paginated by Parameters and ROI. Panel by sides Plot Groups (HV/pSS) along X axis and parameter value along Y axis. Note: Difference will not be presented for this plot	SAC
2.7.	Safety	EFF_F3	Point estimate and 95% CI for ^{11}C-MET PET/CT Derived Parameter of Difference in pSS vs. HV	Page by parameter and ROI. When applicable for a given ROI, the analysis will be separated by side. Plot Subject Groups along X axis and SUV along Y axis. Subheading: 'Parameter: [parameter name]' 'ROI: [ROI name]' Footnote: Difference calculated as pSS-HV. Parameters to include: SUVpeak, SUVmax and SUVmean	SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	Safety	EFF_F6	Posterior Group Means and the Difference in Group Means for ^{11}C-MET PET/CT Parameter by Region	Paginate by parameter and ROI. Panel by side where appropriate. X-axis- include group (HV pSS) and diference Footnote: Difference calculated as pSS-HV. Parameters to include: SUVpeak, SUVmax and SUVmean	SAC
2.9.	Safety	EFF_F7	Ratio of SUV_{peak} (Left/Right) Assessing Asymmetry in ^{11}C-MET PET/CT Parameter	X-axis: Subject Y-axis: Ratio of SUVpeak(left/right) Colour and symbol by subject group Include reference line at Y=1. Footnote: Ratio of 1 (reference line) represents complete symmetry.	SAC
Multiparametric MRI quantitative parameters					
2.10.	Safety	EFF_F1	Plot of Individual Multiparametric MRI Parameters by ROI	Paginated by Parameter and ROI. Column Panel by side. Plot Subject along X axis and parameter value along Y axis. Colour and symbol by subject group.	SAC
2.11.	Safety	EFF_F3	Mean (+/- SE) Plot of MRI Parameters	Paginated by Parameters and ROI. Panel by sides Plot Groups (HV/pSS) along X axis and Parameters along Y axis.	SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	Safety	EFF_F3	Point estimate and 95% CI for Multiparametric MRI Derived Parameter of Difference in pSS vs. HV	Page by Regions of Interest and MRI parameter (i.e Ktrans, D, f, ADC). When applicable for a given ROI, the analysis will be separated by side (left/right/aggregated). Plot Subject Groups along X axis and parameter along Y axis. Panel by side where appropriate. Subheading: 'Parameter: [parameter name]' 'ROI: [ROI name]' Footnote: Difference calculated as pSS-HV.	SAC
2.13.	Safety	EFF_F6	Posterior Group Means and the Difference in Group Means for Multiparametric MRI Parameter by Region	Paginate by parameter and ROI. Panel by side (include left/right/aggregated) where appropriate. X-axis- include group (HV/pSS) and difference Footnote: Difference calculated as pSS-HV. Parameters to include: Ktrans, D, f, ADC. Median will be used for each parameter.	SAC

Note: Above figures will be produced only if data is available.

11.11.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Radioactivity concentrations (static ^{18}F-FDG and ^{11}C-MET)					
3.1.	PK	PKCT1	Summary of ^{11}C-MET Tracer Pharmacokinetic Concentration Data	Paginated by Group and type of blood (Whole and Plasma). Group to include pSS, HV and overall. Subheading: 'Subject group: [group]' 'Blood: [blood type]'	SAC
Radiopharmacokinetic parameters					
3.2.	PK	PKPT1	Summary of Radiopharmacokinetic Parameter – Influx Rate Constant (K_i) from ^{11}C-MET PET/CT	Paginated by Group Group to include pSS, HV and overall. Subheading: 'Subject group: [Group]'	SAC
3.3.	PK	EFF_T3	Summary of correlation between PK modelling index with ^{11}C-MET PET/CT static imaging parameters	Paginated by Group Group to include pSS, HV and overall. Subheading: 'Subject group: [Group]' Change last three column titles to 'SUVpeak' 'SUVmean' and 'SUVmax' respectively. Footnote: Parotid gland side with the highest and lowest uptake values.	SAC

11.11.8. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Radioactivity concentrations (static ^{18}F-FDG and ^{11}C-MET)					
3.1.	PK	PKCF1P	Plot of Individual ^{11}C-MET Tracer Pharmacokinetic Concentration-Time (Linear and Semi-Log)	Paginated by Group and type of blood (Whole and Plasma). Group to include pSS, and HV. Subheading: 'Subject group: [group]' ' Blood: [blood type]'	SAC
Radiopharmacokinetic parameters					
3.2.	PK	EFF_F4	Plot of Individual Radiopharmacokinetic Parameter Influx Rate Constant (K_i) versus Standardised Uptake Value of ^{11}C-MET PET/CT	Paginate by parameters SUVpeak, SUVmean and SUVmax ROI: Parotid Gland Plot Ki along X axis and SUV parameter value along Y axis. Colour by subject group. Panel by sides – side with higher parameter values and side with lower parameter values. Include Pearson's product moment correlation	SAC

11.11.9. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
4.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class	Paginate by subject group	SAC
4.2.	Safety	AE3	Summary of Common Adverse Events by Overall Frequency	Paginate by subject group Footnote: Common defined as 2 or more subjects	SAC
4.3.	Safety	AE15	Summary of Common Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Paginate by subject group Footnote: Common defined as 2 or more subjects	SAC
Serious and Other Significant Adverse Events					
4.4.	Safety	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term	Paginate by subject group	SAC
4.5.	Safety	AE16	Summary of Serious Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Paginate by subject group	SAC

11.11.10. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disease Activity (pSS only)					
5.1.	Safety	EFF_T2	Summary of Disease Activity	List score in the following order: ESSDAI ESSPRI PtGA PhGA Oral dryness Ocular dryness	SAC
5.2.	Safety	EFF_T7	Frequency of ESSDAI Component Scores	Footnote: NA: Not Applicable – Not given as an option for the category in the questionnaire.	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.3.	Safety	EFF_T3	Summary of Correlation Between Disease Activity and Imaging Parameters	Paginate by type of Disease Activity scores. Disease activity score include: ESSDAI and ESSPRI scores Pearson's and Spearman's correlation summary to be provided in the summary table. Imaging parameter from the parotid gland, and include variable for side (high or low, or aggregated). PET/CT parameter: SUVpeak MRI parameter: Median Ktrans, D, IRE, ME , f, ADC, D*; Mean lipid content and gland volume. Subheading 'Disease Activity: [name]'	SAC
5.4.	Safety	EFF_T2	Summary of Laboratory Biomarkers of Disease Activity	Including but not limited to, SS-A, SS-B, C3, C4, CH50, CRP, cryoglobulins, RF, Immunoglobulins, protein elctrophoresi. See 11.3.6 for full list.	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.5.	Safety	EFF_T3	Summary of Correlation Between Laboratory Biomarkers of Disease Activity and Imaging Parameters	Paginate by Laboratory biomarker type. Lab biomarkers: C3, C4 levels and IgG/IgA ratio. Pearson's and Spearman's correlation summary to be provided in the summary table. Imaging parameter from the parotid gland, and include variable for side (high or low, or aggregated). PET/CT and MRI parameter: see Table 5.3 Subheading 'Laboratory Biomarker: [name]'	SAC
Salivary gland					
5.6.	Safety	EFF_T2	Summary of Basal (unstimulated) and Stimulated Salivary Flow Rate (ml/min)	Replace first column with 'Salivary Flow' and add second column 'Group'. Salivary Flow column will include Basal, Stimulated and Difference. Footnote1:' Difference for each individual calculated as stimulated-basal salivary flow at that time point.' Footnote2: 'Salivary flow rate measured in millilitres per minute (ml/min).'	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.7.	Safety	EFF_T3	Summary of Correlation Between Salivary Flow Rate and Imaging Parameters.	Paginate by salivary flow type (i.e. basil, stimulated then difference) Add column for subjects group. Pearson's and Spearman's correlation summary by subject group to be provided in the summary table. Imaging parameter from the parotid gland, and include variable for side (high or low, or aggregated). PET/CT and MRI parameter: see Table 5.3 Subheading 'Salivary Flow: [name]' Footnote: 'Difference for each individual calculated as stimulated-basal salivary flow at that time point.' Footnote2: 'Footnote: 'Salivary flow rate measured in millilitres per minute (ml/min).''	SAC
5.8.	Safety	EFF_T2	Summary of Histological Scores from Salivary Gland Biopsy	First column renamed to 'Histological Scores'. Histological scores include: Maximum lymphocyte focus score Mean lymphocyte focus score Maximum Lymphoid organisation grading Mean Lymphoid organisation grading	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.9.	Safety	EFF_T3	Summary of Correlation Between Histological Scores with Imaging Parameters.	Paginate by type Histological score. Histological scores include: • Maximum lymphocyte focus score • Mean lymphocyte focus score • Maximum Lymphoid organisation grading • Mean Lymphoid organisation grading Pearson's and Spearman's correlation summary to be provided in the summary table. Imaging parameter from the parotid gland, and include variable for side (high or low). PET/CT and MRI parameter: see Table 5.3 Subheading 'Histological Score: [name]'	SAC
Non-Salivary Gland					
5.10.	Safety	EFF_T2	Summary of Strip Length Wet per Minute (mm/min) from Schirmer's Test	Include group, side of eye (most or least), Footnote: 'Ratio calculated as length (mm) paper wet divided by time taken to wet (min). The Ratio is presented as strip length wet per minute. '	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.11.	Safety	EFF_T3	Summary of Correlation Between Length Wet per Minute (mm/min) from Schirmer's Test and Imaging Parameters.	Add column for subjects group. Pearson's and Spearman's correlation summary by subject group to be provided in the summary table. Imaging parameter from the parotid gland, and include variable for side (Left or Right). PET/CT parameter: SUVpeak Subheading 'Schirmer's test: [name]' Footnote: 'Note: Ratio calculated as length (mm) paper wet divided by time taken to wet (min). The Ratio is presented as strip length wet per minute. Note: The side of the eye for the Schiremr's test is correlated with the same side of the imaging parameter.'	SAC

11.11.11. Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Association between clinical and imaging parameters of the salivary gland					
5.1.	Safety	EFF_F4	Plot of Basal Salivary Flow Rate vs Imaging Parameters in the Parotid Gland	Paginate by parameter. Symbol by subject group where applicable Panel plot: column for the side of gland (low, high and aggregated) PET/CT parameter: SUVpeak MRI parameter: Median Ktrans, D, IRE, ME , f, ADC, D*; Mean lipid content and gland volume. Subheading 'Imaging Parameter: [imaging technique] [parameter name]' Include Pearson's product moment correlation for each group. Footnote: 'Salivary flow rate measured in millilitres per minute (ml/min).'	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.2.	Safety	EFF_F4	Plot of Stimulated Salivary Flow Rate vs Imaging Parameters in the Parotid Gland	Paginate by parameter. Symbol by subject group where applicable Panel plot: column for the side of gland (low, high and aggregated) PET/CT and MRI parameter: see Figure 5.1 Subheading 'Imaging Parameter: [imaging technique] [parameter name]' Include Pearson's product moment correlation Footnote: 'Salivary flow rate measured in millilitres per minute (ml/min).'	SAC
5.3.	Safety	EFF_F4	Plot of Difference (Stimulated-Basal) in Salivary Flow Rate vs Imaging Parameters in the Parotid Gland	Paginate by parameter. Symbol by subject group where applicable Panel plot: column for the side of gland (low, high and aggregated) PET/CT and MRI parameter: see Figure 5.1 Subheading 'Imaging Parameter: [imaging technique] [parameter name]' Include Pearson's product moment correlation	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.4.	Safety	EFF_F4	Plot of ESSDAI score vs Imaging Parameters in the Parotid Gland	Paginate by parameter. Panel plot: column for the side of gland (low, high and aggregated) PET/CT and MRI parameter: see Figure 5.1 Subheading 'Imaging Parameter: [imaging technique] [parameter name]' Include Pearson's product moment correlation	SAC
5.5.	Safety	EFF_F4	Plot of ESSPRI score vs Imaging Parameters in the Parotid Gland	Paginate by parameter. Panel plot: column for the side of gland (low, high and aggregated) PET/CT and MRI parameter: see Figure 5.1 Subheading 'Imaging Parameter: [imaging technique] [parameter name]' Include Pearson's product moment correlation	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.6.	Safety	EFF_F4	Plot of Laboratory Biomarker of Disease Activity vs Imaging Parameter in the Parotid Gland	Paginate by Parameter and Laboratory biomarker type. Lab biomarkers: C3, C4 levels and IgG/IgA ratio. Panel plot: column for the side of gland (low, high and aggregated) PET/CT and MRI parameter: see Figure 5.1 Subheading: 'Imaging Parameter: [imaging technique] [parameter name]' 'Laboratory Biomarker: [name]' Include Pearson's product moment correlation	SAC
Association between histological and imaging parameters of the salivary gland					
5.7.	Safety	EFF_F4	Plot of Imaging Parameters vs Histological Scores from Salivary Gland Biopsy	Paginate by parameter and histological score. Panel by side of the gland: low, high, and aggregated PET/CT and MRI parameter: see Figure 5.1 Subheading: 'Imaging Parameter: [imaging technique] [parameter name]' 'Histological Score: [name]' Include Pearson's product moment correlation	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Association between lacrimal gland and imaging parameters					
5.8.	Safety	EFF_F4	Plot of Imaging Parameters vs Length Wet per Minute (mm/min)	Paginate by parameter. Panel plot: column for side of gland/eye (Left and Right) Symbol by subject group where applicable ROI: Lacrimal gland . PET/CT parameter: SUVpeak Subheading: 'Imaging Parameter: [imaging technique] [parameter name]' Include Pearson's product moment correlation Note: Ratio calculated as length (mm) paper wet divided by time taken to wet (min). The Ratio is presented as strip length wet per minute. Note: The side of the eye for the Schirmer's test is correlated with the same side of the imaging parameter	SAC

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Association between imaging parameters					
5.9.	Safety	EFF_F5	Plot of Imaging Parameters vs Imaging Parameters Obtained from Different Imaging Technique.	Symbol by subject group where applicable. Panel by side of the gland : low/high/aggregated Paginate by plots type with subheading of parameters being compared: FDG (SUVmean) vs CMET(SUVmean), FDG(SUVmax) vs CMET(SUVmax), FDG(SUVpeak) vs CMET(SUVpeak), CMET(SUVpeak) vs MRI(Mean Lipid content) FDG(SUVpeak) vs MRI(Mean Lipid Content) MRI(Mean Lipid Content) vs MRI(Median; Ktrans, IRE, ME, D, f, D* and ADC)	SAC

11.11.12. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failures		SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC
Protocol Deviations					
3.	Safety	DV2	Listing of Important Protocol Deviations		SAC
4.	Safety	IE3	Listing of Subjects with Inclusion/ Exclusion Criteria Deviations		SAC
Populations Analysed					
5.	Screened	SP3	Listing of Subjects Excluded from Any Population		SAC
Demography					
6.	Safety	DM2	Listing of Demographic Characteristics		SAC
7.	Safety	DM9	Listing of Race		SAC
Prior and Current Medical conditions					
8.	Safety	MH2	Listing of Medical Conditions	Include family history of cardiovascular disease	SAC
Concomitant Medications					
9.	Safety	CP_CM3	Listing of Concomitant Medications		SAC
Adverse Events					
10.	Safety	CP_AE8	Listing of All Adverse Events		SAC
11.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
13.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
14.	Safety	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study		SAC
Study procedure AEs and SAEs					
15.	Safety	AE8CP	Listing of Adverse Events Related to Study Procedure	This includes contrast related AEs	SAC
Chemistry					
16.	Safety	LB5	Listing of Clinical Chemistry Values		SAC
Hematology					
17.	Safety	LB5	Listing of Hematology Values		SAC
Urinalysis					
18.	Safety	UR2A	Listing of Urinalysis Data		SAC
All Laboratory					
19.	Safety	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Concern/Potential Clinical Importance	Footnote: Contains laboratory test data for continuous test results only.	SAC
Vital Signs					
20.	Safety	VS4	Listing of All Vital Signs		SAC
21.	Safety	VS4	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

11.11.13. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
22.	Safety	EFF_L4	Listing of Tobacco Use		SAC
23.	Safety	EFF_L5	Sjogren's Syndrome Disease History	Sjogren's Syndrome patients only	SAC
Safety					
24.	Safety	EFF_L6	Listings of Antibody Test Results	Sjogren's Syndrome patients only	SAC
25.	Safety	EFF_L8	Listing of Dental Work History		
^{18}F-FDG PET/CT semi-quantitative parameters					
26.	Safety	EFF_L1	Listing of ^{18}F-FDG PET/CT Parameters		SAC
^{11}C-MET PET/CT semi-quantitative parameters					
27.	Safety	EFF_L1	Listing of ^{11}C-MET PET/CT Parameters		SAC
28.	Safety		RAW SAS Output of Statistical Analysis Results for Difference in ^{18}F-FDG PET/CT Parameter		SAC
29.	Safety		RAW SAS Output of Bayesian Analysis Results of ^{18}F-FDG PET/CT Parameter		SAC
30.	Safety	EFF_L7	Listing of Totality of Meal Ingested		
Multiparametric MRI quantitative parameters					
31.	Safety	EFF_L1	Listing of MRI Parameters		SAC
32.	Safety		RAW SAS Output of Statistical Analysis Results for Difference in MRI Parameter		SAC
33.	Safety		RAW SAS Output of Bayesian Analysis Results for MRI Parameter		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Contrast Agent					
34.	Safety	EFF_L2	Listings of Tracer and Contrast Agent Administration Volume		SAC
Radioactivity concentrations (static ^{18}F-FDG and ^{11}C-MET)					
35.	PK	PKCL1P	Listing of ^{18}F-FDG Tracer Pharmacokinetic Concentration Data	Paginated by Whole Blood and Plasma	SAC
36.	PK	PKCL1P	Listing of ^{11}C-MET Tracer Pharmacokinetic Concentration-Time Data	Paginated by Whole Blood and Plasma	SAC
Radiopharmacokinetic Parameters					
37.	PK	PKPL1P	Listing of Influx Rate Constant(K_i)		SAC
Disease index (pSS patients only)					
38.	Safety	EFF_L3	Listing of Blood Biomarkers of Disease Activity		SAC
39.	Safety	EFF_L3	Listing of ESSDAI Scores and Components	Include components scores then final scores – this will be a new column after 'actual time' column consisting of component names and final score. Domain score should include both the category and score (i.e. Low=2)	SAC
40.	Safety	EFF_L3	Listing of ESSPRI Score and Components	Include components scores then final scores – this will be a new column after actual time consisting of component names and final score.	SAC
41.	Safety	EFF_L3	Listing of Patients' Global Assessment		SAC
42.	Safety	EFF_L3	Listing of Physician's Global Assessment (VAS 0-100mm)		SAC
43.	Safety	EFF_L3	Listing of Oral Dryness Numeric Rating		SAC
44.	Safety	EFF_L3	Listing of Ocular Dryness Numeric Rating		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Salivary Gland Specific Endpoints					
45.	Safety	EFF_L3	Listing of Basal Salivary Flow Rate (ml/min)		SAC
46.	Safety	EFF_L3	Listing of Stimulated Salivary Flow Rate (ml/min)		SAC
47.	Safety	EFF_L3	Listing of Histological Score from Salivary Gland Biopsy	Include a column for cell type.	SAC
Non-salivary gland					
48.	Safety	EFF_L3	Listing of Paper Wetted and Time to Wet from Schirmer's Test	Include column (last) for change from baseline.	SAC

11.12. Appendix 12: Example Mock Shells for Data Displays

Example : EFF_T1
Protocol : 203818
Population : Safety

Table 2.1
Summary of ^{18}F-FDG PET/CT parameters

Parameter: Parameter 1

Region of Interest	Sides	Group	N	n	Mean	SD	SE	Q1	Median	Q3	Min.	Max.
ROI 1	Low	pSS	xx	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x	xx.x	xx	xx
		HV	xx	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x	xx.x	xx	xx
	High	pSS	xx	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x	xx.x	xx	xx
		HV	xx	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x	xx.x	xx	xx
ROI 2	NA	pSS	Xx	Xx	xx.x	xx.xx	xx.xx	xx.x	xx.x	xx.x	xx	Xx
			xx	xx	xx.x	xx.x						

Note: NA: Sides are not applicable for all ROI.

Programming Note: Include Groups as a separate column next to Sides for 11C-MET PET/CT parameters summary.

Example : EFF_T2
Protocol : 203818
Population : Safety

Table X.X

Summary of Disease Activity (pSS only)

Disease Activity	N	n	Mean	SD	Median	Minimum	Maximum
ESSDAI score							
ESSRPI score							
Patient Global assessment (VAS)							
Physician Global Assessment (VAS)							
Oral dryness numerical rating							
Ocular dryness numerical rating							

Example : EFF_T3
Protocol : 203818
Population : Safety

Table x.x

Summary of Correlation Between Disease Activity and Imaging Parameters

Disease Activity: [name of index]

Scan / Parameter	Side	Pearson's correlation / 95% CI	Spearman's correlation / 95% CI
^{11}C-MET / SUVpeak	High	x.xx / (x.xx, x.xx)	x.xx / (x.xx, x.xx)
	Low	x.xx / (x.xx, x.xx)	x.xx / (x.xx, x.xx)
F-FDG / SUVpeak	High	x.xx / (x.xx, x.xx)	x.xx / (x.xx, x.xx)
	Low	x.xx / (x.xx, x.xx)	x.xx / (x.xx, x.xx)
MRI / Ktrans	High	x.xx / (x.xx, x.xx)	x.xx / (x.xx, x.xx)
	Low	x.xx / (x.xx, x.xx)	x.xx / (x.xx, x.xx)

Example: EFF_T4
Protocol: 203818
Population: Safety

Table x.xx

Point estimate and 95% CI for [imaging method] Derived Parameter of Difference in pSS vs. HV

ROI: [ ] Side: [ ]

N	Group	n	Mean	Standard Error	Difference from HV	95% CI for Difference (Lower, Upper)
xx	HV	xx	x.xx	x.xxx		
xx	pSS	xx	x.xx	x.xxx	x.xx	(x.xx, x.xx)
xx	HV	xx	x.xx	x.xxx		
xx	pSS	xx	x.xx	x.xxx	x.xx	(x.xx, x.xx)

Example: EFF_T5
Protocol: 203818
Population: Safety

Summary of the Posterior Distribution of the Ratio and Difference of Group Means for [Imaging method] parameters by Region

					Posterior distribution					
Parameter	ROI	Group	Prior Distribution for Θ	Value of σ used in then model	Mean	SD	Median	25th quartile	75th quartile	95% Credible Interval
Mean SUV	Parotid Gland	pSS (N=xx)	normal(0, sd = 100)	1	x.xx	x.xx	x.xx	x.xx	x.xx	(x.xx,x.xx)
		HV (N=xx)	normal(0, sd = 100)	1	x.xx	x.xx	x.xx	x.xx	x.xx	(x.xx,x.xx)
		Difference								
					x.xx	x.xx	x.xx	x.xx	x.xx	(x.xx,x.xx)
		Ratio								
					x.xx	x.xx	x.xx	x.xx	x.xx	(x.xx,x.xx)
	Submandibular Gland									

pSS=primary Sjogren's Syndrome patients HV=Health Volunteers, ROI = Region of Interest

Number of MCMC iterations, excluding the burn-in iterations = 5,000. Number of burn-in iterations = 10,000

The PET parameters are assumed to follow a normal distribution with unknown mean Θ and known variance σ^2 (i.e. $N(\Theta, \sigma^2)$) .

Difference calculated as pSS-HV and ratio as pSS/HV. 95% credible intervals based on the highest posterior density interval.

Example: EFF_T6
Protocol: 203818
Population: Safety

Posterior Probability that the Ratio and Difference of Group Means for [Imaging Method] Parameter Exceeds a Certain Value, by Region

Parameter (units)	Region	P(ratio) > 0.5	P (ratio) > 1	P(ratio) > 1.5	P(Difference) > 0
Mean SUV					

Note: P(ratio) > 1 is the probability that the posterior ratio of group means exceeds 1 based on 5,000 simulated posterior predicted values. *Ratio of pSS patients to Healthy Volunteers and difference of pSS-HV.*

Example : EFF_T7
Protocol : 203818
Population : Safety

Table X.X

Summary of ESSDAI Component Scores
Activity Level

Domain	No	Low	Moderate	High
Constitutional	n(%)	n(%)	n(%)	NA
Lymphadenopathy	n(%)	n(%)	n(%)	n(%)
Glandular	n(%)	n(%)	n(%)	NA
Articular	n(%)	n(%)	n(%)	n(%)
Cutaneous	n(%)	n(%)	n(%)	n(%)
Pulmonary	n(%)	n(%)	n(%)	n(%)

Renal	n(%)	n(%)	n(%)	n(%)
Muscular	n(%)	n(%)	n(%)	n(%)
PNS	n(%)	n(%)	n(%)	n(%)
CNS	n(%)	NA	n(%)	n(%)
Haematological	n(%)	n(%)	n(%)	n(%)
Biological	n(%)	n(%)	n(%)	NA

Example : EFF_L1
Protocol : 203818
Population : Safety

Listing xx
Listing of ^{18}F-FDG PET/CT Parameters

		Imaging Parameter				
Subject	ROI	SUV_{mean}	SUV_{peak}	SUV_{max}	TR	TIV
xxxxx	Parotid Left					
	Parotid Right					
	……					

SUV= Standardised Uptake Value, TR = tissue-to-reference ratio ,TIV = total inflammatory volume.(description of all Parameter)

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Example : EFF_L2
Protocol : 203818
Population : Safety

Listing No. XX

Listing of Tracer and Contrast Agent Administration Volume

Subjid	Visit	Contrast Agent/Tracer	Volume of Administration (Unit)
xxx	Visit1	Gadolinium	x
	Visit1	C-MET	x
	Visit2	FDG	x

Example: EFF_L3
Protocol: 203818
Population: Safety

Listing X
Listing of Patients' Global Assessment (VAS 0-100mm)

Subj.	Planned Relative Time	Actual date/time	Study Day	Score
PPD	Baseline	PPD /14:00:00	1	100
	Baseline	/14:00:00	1	98

Listing 22
Listing of Tobacco Use

Example:
Protocol:
Page 1 of n
Population:

EFF_L4
203818
Safety

Site ID/ Subject ID	Smoking history	Last smoke	Average cigarettes per day
XX/XXXXX	Never	NA	
XX/XXXXX	Current	NA	
XX/XXXXX	Former	YYYY-MM-DD	

Example: EFF_L5
Protocol: 203818
Population:

Listing 23
Sjogren's Syndrome Disease History

Safety

Site ID/ Subject ID	Date of Formal pSS Diagnosis	Duration since Formal Diagnosis (months)	Classification
XX/XXXXX	YYYY-MM-DD	XX.X	Ocular symptoms Oral symptoms
XX/XXXXX	YYYY-MM-DD	xx.x	Histopathology Salivary gland involvement
XX/XXXXX			

Example: EFF_L6
Protocol: 203818
Population:

Listing 24
Listing of Antibody Test Result

Safety

Site ID/ Subject ID	Date of assessment	Test	Result
XX/XXXXX	YYYY-MM-DD	Total Ig	x.xx
		IgG	x.xx
		IgA	x.xx
		IgM	No result
XX/XXXXX	YYYY-MM-DD	Total Ig	x.xx
		IgG	x.xx
		IgA	x.xx
		IgM	No result
XX/XXXXX			

Example: EFF_L7
Protocol: 203818
Population:

Listing 28
Listing of Totality of Meal Ingested

Safety

Site ID/ Subject ID	Meal start time	Meal end time	Duration	Meal ingested
XX/XXXXX	HH:MM	HH:MM	x.xx	1-25%
XX/XXXXX	HH:MM	HH:MM	x.xx	76-100%
XX/XXXXX	HH:MM	HH:MM	x.xx	Yes

Example: EFF_L8
Protocol: 203818
Population:

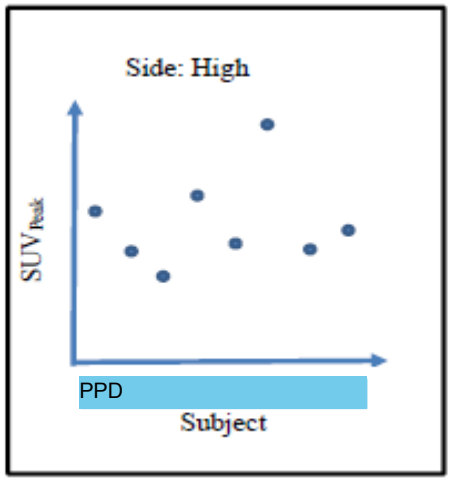
Site ID/ Subject ID	Dental Work	Yes/No - Location
XX/XXXXX	Non-metallic filling or crowns	No
	Other fillings	Yes – Top Left

Page 1 of n
Safety

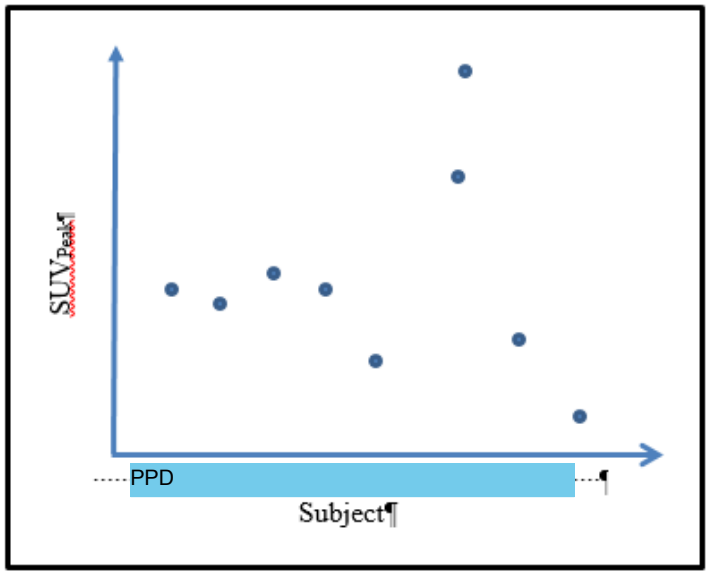
Example : EFF_F1
Protocol : 203818
Population : Safety

Figure 2.2
Plot of Peak Standardised Uptake Value (SUV_{peak}) from ^{18}F-FDG PET/CT by ROI

ROI : Parotid Gland



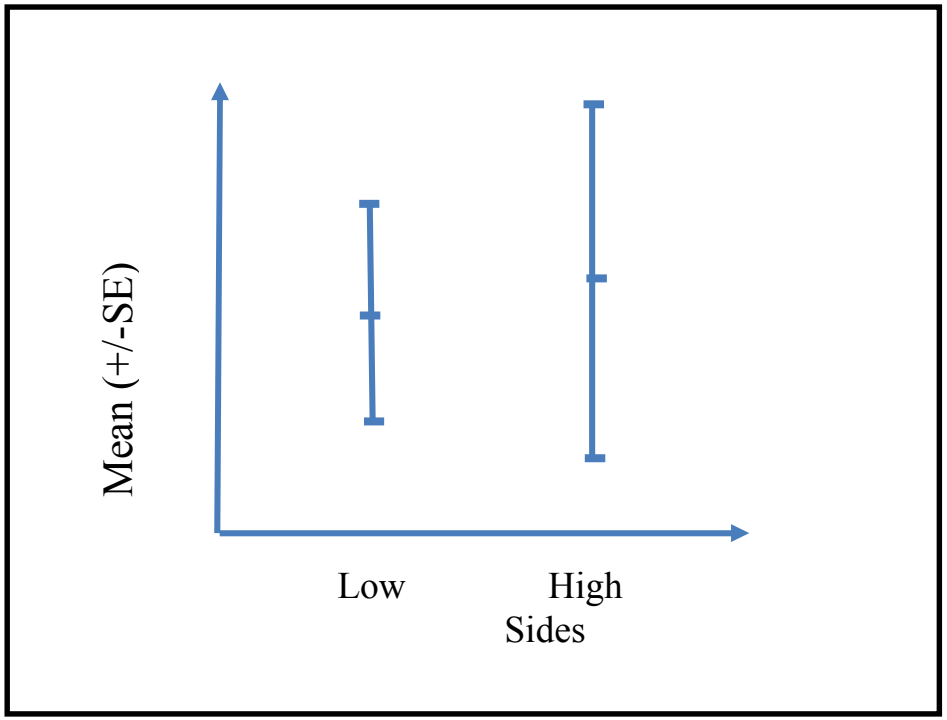
Programming Note: Panel plot when the ROI is split by side (above) otherwise single plot (below)



Example : EFF_F2
Protocol : 203818
Population : Safety

Figure 2.x
Mean (+/- SE) of ^{18}F-FDG PET/CT Parameters.

Parameter: [Parameter 1] ROI: [ROI 1]

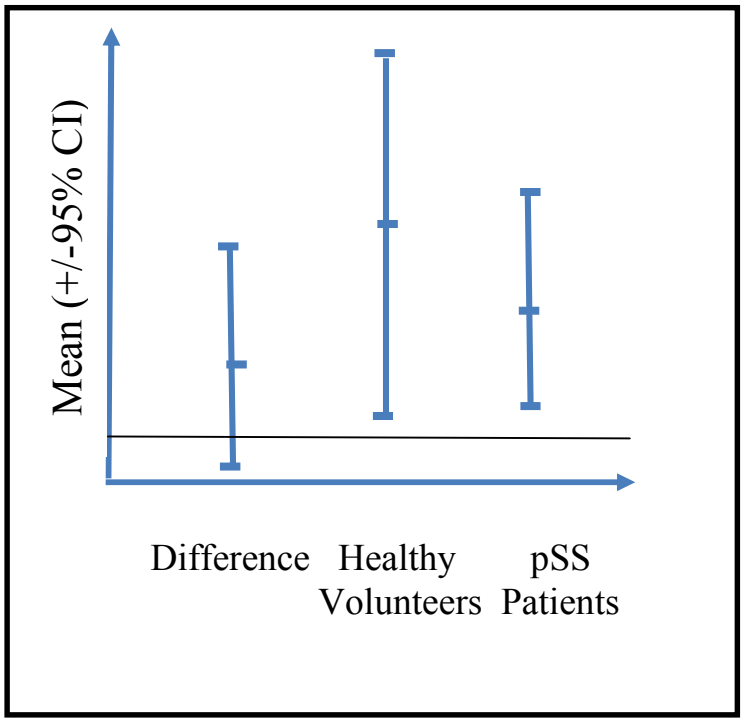


Example : EFF_F3
Protocol : 203818
Population : Safety

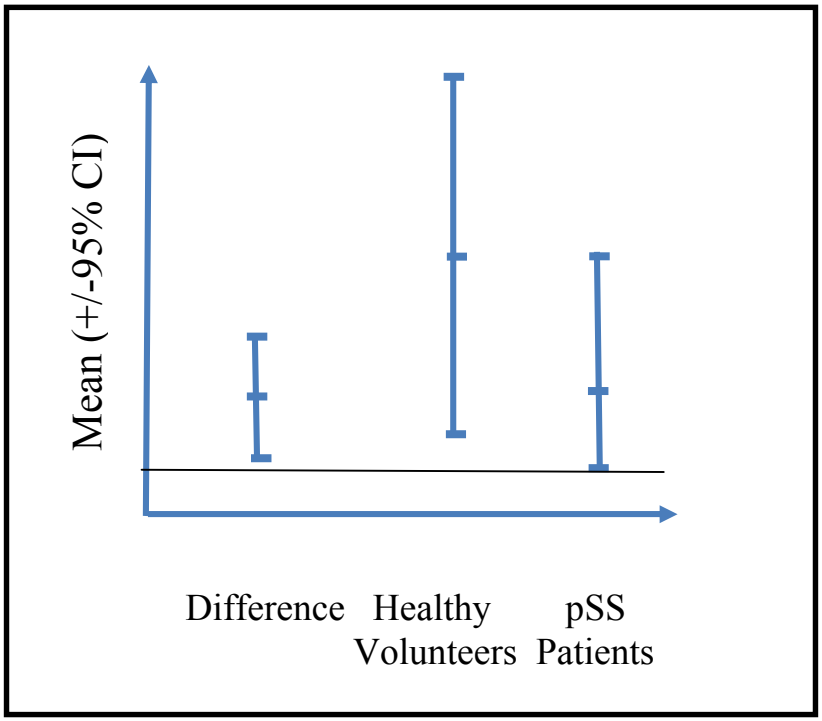
Figure 2.x

Point estimate and 95% CI for [imaging method] derived parameters of Difference in pSS vs. HV
Parameter: [Parameter 1] ROI: [ROI 1]

Side: Low



Side: High

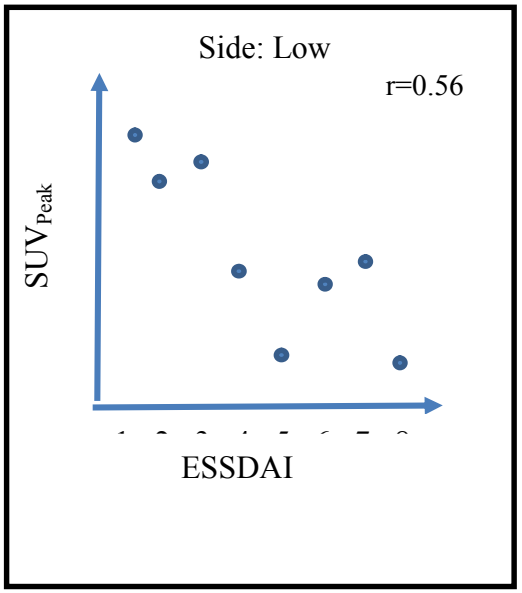


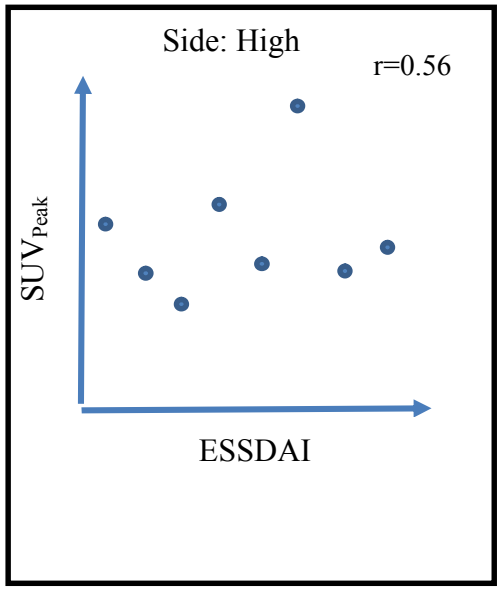
Example : EFF_F4
Protocol : 203818
Population : Safety

Figure x.x

Plot of Disease Activity scores vs Imaging Parameters in the Parotid Gland

Parameter: SUVpeak Disease Activity: ESSDAI score





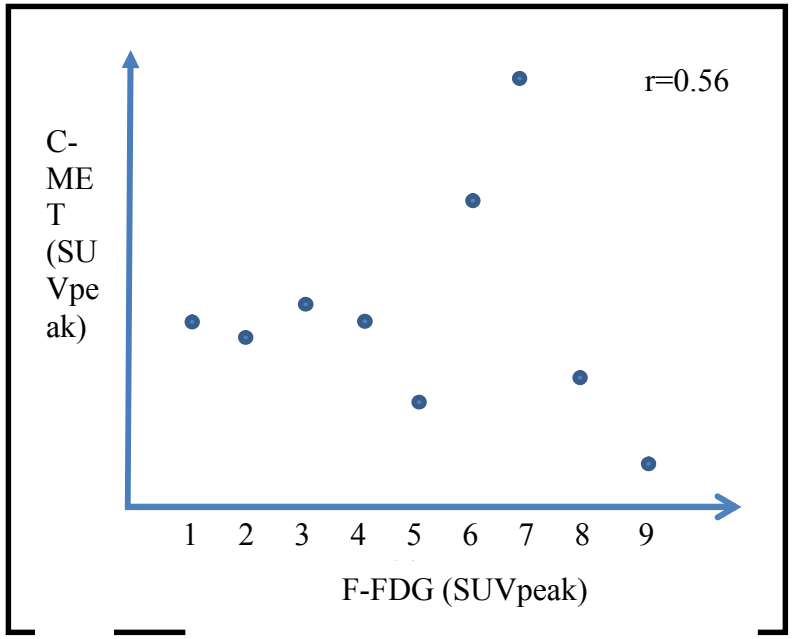
r: Pearson's product moment correlation

Example : EFF_F5
Protocol : 203818
Population : Safety

Figure x.x

Plot of Imaging Parameters vs Imaging Parameters Obtained from Different Imaging Technique.

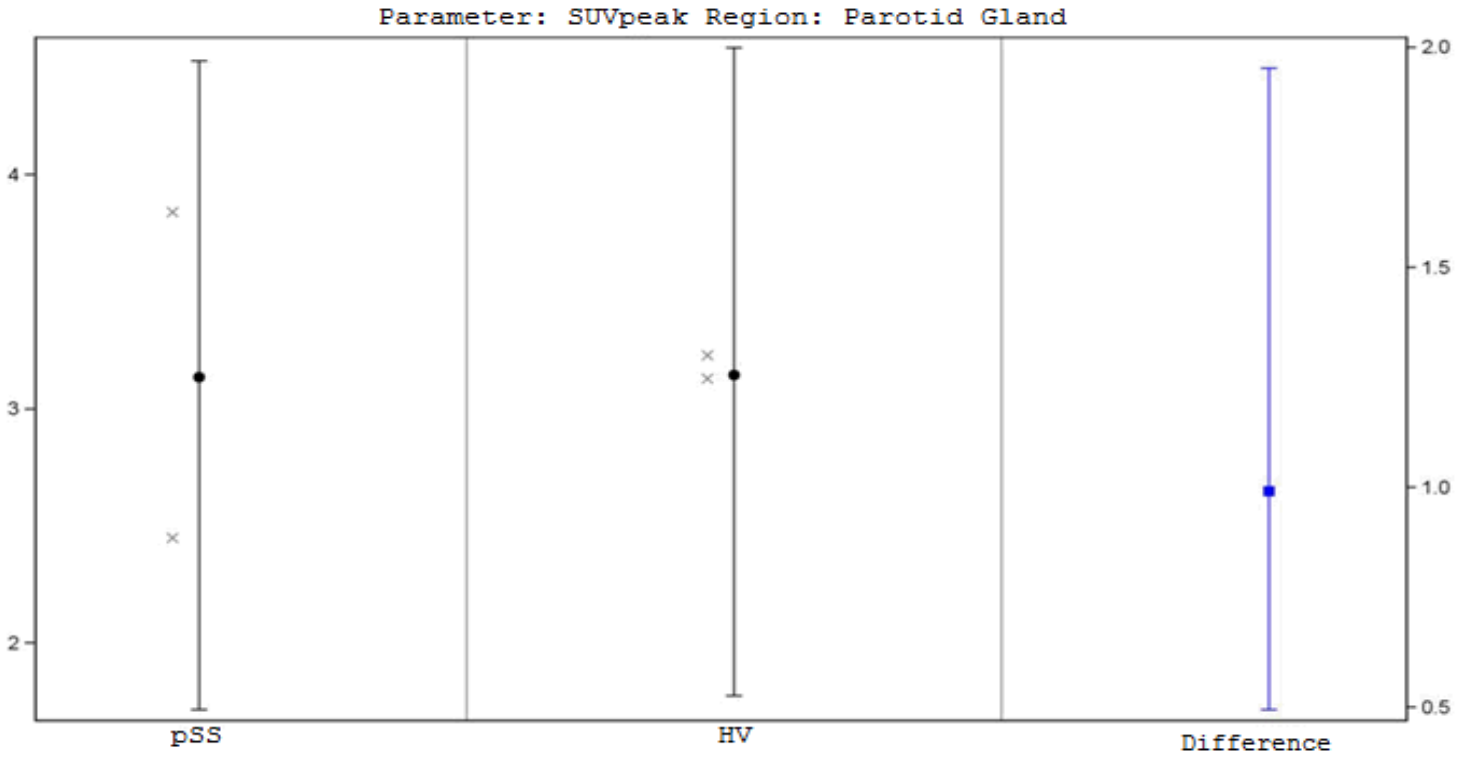
Parameter: C-MET(SUVpeak) vs F-FDG (SUVpeak)



r: Pearson's product moment correlation

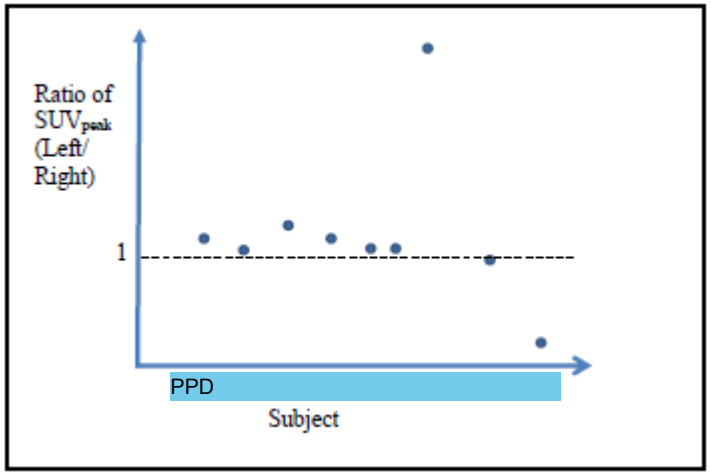
Example : EFF_F6
Protocol : 203818
Population : Safety

Figure x.x
Posterior Group Means and the Difference in Group Means for [Imaging method] Parameter by Region



Example : EFF_F7
Protocol : 203818
Population : Safety

Figure x.x
Ratio of SUV_{peak} (Left/Right) Assessing Asymmetry in ^{11}C-MET PET/CT Parameter



Ratio of 1 (reference line) represents complete symmetry.