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

Title	:	Reporting and Analysis Plan for Exploration of the peripheral immune system in subjects with New Onset T1 Diabetes (NOT1D)
Compound Number	:	None
Effective Date	:	09-Jun-2107

Description :

- The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and outputs for the second interim analysis after the first 5 healthy volunteers (HVs) and 5 NOT1D subjects, The primary purpose of this interim analysis will be to facilitate decision making and study design for a potential follow-up interventional study.

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Approved by:

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and outputs for the second interim analysis after the first 5 healthy volunteers (HVs) and 5 NOT1D subjects, the primary purpose of this interim analysis will be to facilitate decision making and study design for a potential follow-up interventional study.
Protocol	• This RAP is based on the protocol amendment 3 (Dated: 07-Mar-2017) of study OTX203158 (GSK Document No.: 2015N246275_03] and eCRF Version 1.0.
Primary Objective / Endpoint	• To assess the frequency and phenotype of leukocyte subsets in iLN biopsies and peripheral blood in HVs and NOT1D subjects, measured by: o Absolute number and/or proportion of leukocyte subset in iLN biopsies and peripheral blood.
Secondary Objectives / Endpoint	• To assess the frequency and phenotype of leukocyte subsets in iLN core biopsies and iLN fine needle aspirates in HVs and NOT1D subjects measured by: o Absolute number and/or proportion of leukocyte subsets in iLN core biopsies and iLN fine needle aspirates. • To assess the safety and tolerability of iLN biopsy as well as expectations and experience of the biopsy procedure. o Number of AEs and SAEs following lymph node biopsy procedure. Descriptive data obtained by a questionnaire on the acceptability of iLN biopsy in research setting.
Study Design	• A non-drug treatment study to compare differences in immune cells derived from iLN and peripheral blood of NOT1D subjects and HVs. Up to 15 evaluable NOT1D subjects and up to 15 evaluable HVs will be enrolled. The first interim analysis will assess the first 5 HVs, so as to determine the quality and quantity of cells. The second interim will assess the first 5 HVs and 5 NOT1D subjects Following the interim, for the remainder of the study the team will seek to match NOT1D subjects to HVs at a group level according to the number of subjects for each gender and the distribution of age within gender.
Planned Analyses	• Interim 1, Interim 2, Final
Analysis Populations	• Safety, Per Protocol, Core Biopsy, Fine Needle Aspirate Biopsy, Biopsy, Blood
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	• The absolute values and proportion of flow cytometry cell counts of the iLN Biopsies and peripheral blood will be analyzed using generalized linear mixed models adjusting for group, sample type and the interaction of group and sample type. The model will include a subject random effect.

Overview	Key Elements of the RAP
Secondary Analyses	• As per primary using only iLN Biopsy. • In addition, safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.
Exploratory Analyses	• For this RAP, no exploratory endpoints will be described and details will be provided in subsequent RAPs.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

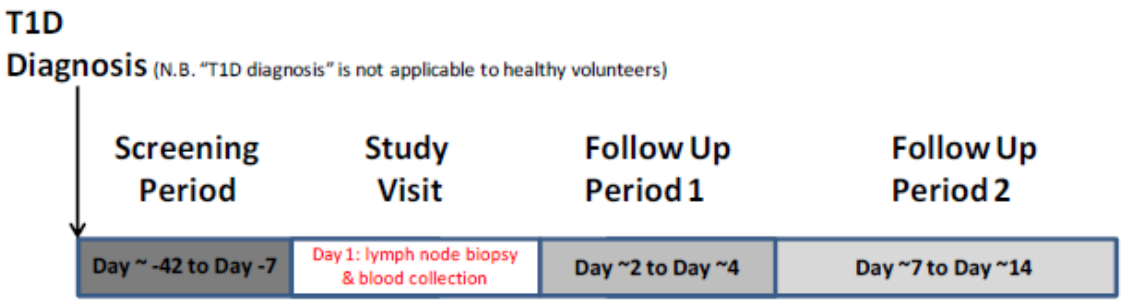
There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 3 (Dated: 06-Mar-2017).

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
1) To assess the frequency and phenotype of leukocyte subsets in iLN and peripheral blood in HVs and NOT1D subjects	• Absolute number and/or proportion of leukocyte subsets in iLN and peripheral blood
Secondary Objectives	**Secondary Endpoints**
1) To assess the frequency and phenotype of leukocyte subsets in iLN core biopsies and iLN fine needle aspirates in HVs and NOT1D subjects	• Absolute number and/or proportion of leukocyte subsets in iLN core biopsies and iLN fine needle aspirates
2) To assess the safety and tolerability of iLN biopsy as well as expectations and experience of the biopsy procedure	• Number of AEs and SAEs following lymph node biopsy procedure • Descriptive data obtained by a questionnaire on the acceptability of iLN biopsy in research setting.
Exploratory Objectives*	**Exploratory Endpoints**
1) To assess suppression activity of T regulatory lymphocytes from the iLN and peripheral blood in HVs and NOT1D subjects	• Relative levels of T lymphocyte suppressive activity of cells from iLN and peripheral blood respectively
2) To assess the frequency of cytokine-producing lymphocytes in HVs and NOT1D subjects	• Proportion of lymphocyte populations producing pro-inflammatory and/or anti-inflammatory cytokines in iLN and peripheral blood
3) To assess clonal expansion of T and B lymphocyte populations in HVs and NOT1D subjects	• Comparison of TCR and BCR usage in lymphocytes in iLN and peripheral blood
4) To assess the gene expression fingerprint of auto-antigen specific lymphocytes in HVs and NOT1D subjects	• Gene expression levels of sorted auto antigen stimulated T lymphocyte populations in iLN and peripheral blood
5) To assess the phenotype and transcriptomic fingerprint of stromal cells from iLN core biopsy samples in HVs and NOT1D subjects	• Absolute number and/or proportion of stromal cell subsets and gene expression levels of stromal cell subsets from iLN core biopsy samples

* The Exploratory objectives / endpoints are listed in order of priority and the conduct of any experimental assays will be dependent on the material available (i.e. number of cells obtained) from iLN biopsies and peripheral blood.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	A multi-centre, non-drug treatment study to compare differences in immune cells derived from iLN and peripheral blood of NOT1D subjects and HVs.
Dosing	• Not applicable (non-drug interventional study)
Treatment Assignment	• Not applicable
Interim Analysis	Interim analyses will be carried out at the following timepoints: • After at least 5 HVs have been biopsied. • An interim analysis will be carried out after the recruitment of 5 evaluable HVs and 5 evaluable NOT1D subjects. These are further described in Section 3.1.

2.4. Statistical Hypotheses

This study is designed to explore the phenotype of immune cells in the iLN and peripheral blood (such as, but not restricted to PBMCs) of NOT1D subjects compared to HVs.

There are no formal hypotheses being tested due to the exploratory nature of the study. Primary comparisons of NOT1D subjects to HVs will be made using an estimation approach, providing point estimates and confidence intervals.

Secondary comparisons of biopsy methods will be made within NOT1D subjects and HVs using an estimation approach:

- iLN biopsies will be carried out by two related methods, fine-needle aspirate (FNA) and core biopsy sampling:
- If sufficient numbers of cells to meet the cell number requirements of the primary endpoint are obtained by both biopsy methods, the primary endpoint analysis will

be carried out independently for each biopsy method, otherwise only the biopsy method for which sufficient numbers of cells were obtained will be used for primary analysis.

- If no meaningful differences between biopsy methods are observed, material from both biopsy methods may be pooled to meet exploratory objectives 1, 2, 3 and 4. Material from fine-needle aspirate and core biopsies will not be pooled unless supported by the comparison described above.
- If meaningful differences in the proportion of leukocyte subsets between cells derived from each biopsy method are observed, then:
    - If sufficient number of core biopsy derived cells are available, these will be analysed for exploratory objectives 1 and 2.
    - Fine needle aspirate derived cells will be used to meet exploratory objectives 3 and 4. If insufficient number of core biopsy derived cells are available to meet exploratory objectives 1 and 2, then fine needle aspirate derived cells may be used to meet either or both of those exploratory objectives.

A graphical representation of the comparisons are shown in Figure 1.

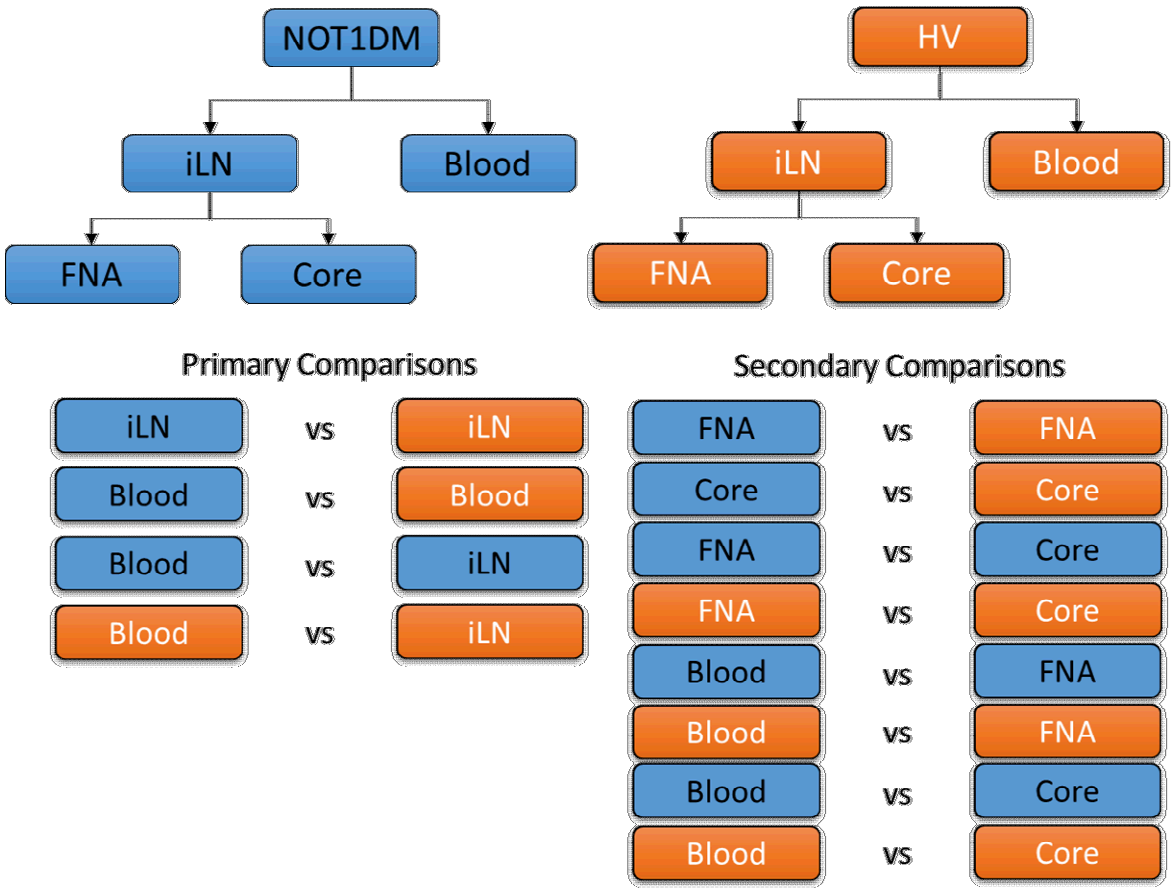


Figure 1 - Graphical representation of comparisons

3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Interim Analysis 1

A data look will be carried after the recruitment of a cohort of up to 5 HVs to determine if the quality and quantity of cells derived from either fine needle aspirate or core biopsy of the inguinal lymph node and from peripheral blood are likely to be sufficient to continue the study to meet its primary objective.

The decision rules for the study to continue are:

- Peripheral blood yields > $1x10e^6$ cells, and
- Yield from either iLN biopsy samples > $1x10e^6$ cells.

In addition, the data from the interim analysis will be used to explore the assumptions and feasibility of the primary statistical analysis, and may also be used for pre-programming of outputs for the final analysis.

If the decision is taken to stop the study at the interim, the full safety outputs plus listings of other collected data will be produced.

3.1.2. Interim Analysis 2

An interim analysis will be carried out after the recruitment of 5 evaluable HVs and 5 evaluable NOT1D subjects. The primary purpose of this interim analysis will be to facilitate decision making and study design for a potential follow-up interventional study.

In addition, the interim analysis results would also help to enable prioritization of the exploratory assays and to facilitate the final RAP. Due to uncertainty around variability and precision, the primary analyses described in Section 7 will be performed in order to re-assess the precision of estimates for the comparisons of interest.

3.2. Final Analyses

The final planned primary 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
Safety	• Comprised of all subjects who complete any study assessment	• Study Population • Safety
Core Biopsy	• Subjects in the 'Safety' population for whom at least one lymph node core biopsy was taken	• Biomarker
Fine needle aspirate Biopsy	• Subjects in the 'Safety' population for whom at least one lymph node fine needle aspirate biopsy was taken	• Biomarker
Biopsy	• Subjects in both 'Core Biopsy' and 'fine needle aspirate biopsy' populations	• Biomarker
Blood	• Subjects in the 'Safety' population for whom one blood sample was taken for analysis of cells derived from peripheral blood.	• Biomarker
Per Protocol	• Subjects in the 'Safety' Population who were compliant with the Protocol	• Biomarker

NOTES :

- Please refer to
- Appendix 10: List of Data Displays which details the population to be used for each displays 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 summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).
    - 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 summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.
- Analyses may be repeated on the Per Protocol population if deemed important.

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.

There are planned examination of covariates and subgroups.
There are no planned adjustments made for multiple centres in this study.
There are no planned adjustments for multiple comparisons or multiplicity.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Model Checking and Diagnostics for Statistical Analyses
10.8	Appendix 8: Biomarker Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in
Appendix 10: List of Data Displays

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		
Reasons for Screen Failure	Y		Y
Subjects by Country and Centre	Y		
Reasons for Subject Withdrawal			Y
Protocol Deviations			
Important Protocol Deviations			Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Populations Analysed			
Study Populations and Exclusions	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Race and Racial Combinations	Y		Y [1]
Race and Racial Combination Details	Y		
Prior and Concomitant Medications			
Past Medical Conditions	Y		
Concomitant Medications	Y		Y

NOTES :

- Y = Yes display generated.

[1] Listing of race.

6.1.1. Interim Analysis 1

No study population analyses will be produced for the first interim analysis.

6.1.2. Interim Analysis 2

No study population analyses will be produced for the first interim analysis.

7. PRIMARY STATISTICAL ANALYSES

7.1. Biomarker Analyses

7.1.1. Overview of Planned Biomarker Analyses

The primary biomarker analyses will be based on the 'Safety' population, unless otherwise specified.

Between group (HV vs NOT1D) comparisons will use data from all subjects who have at least one evaluable sample from either method. Between method comparisons and analyses will only be performed in subjects who provide sufficient cells from both methods in each pairwise comparison (as shown in Figure 1).

If sufficient numbers of cells to meet the cell number requirements of the primary endpoint are obtained by both biopsy methods, the primary endpoint analysis will be carried out independently for each biopsy method, otherwise only the biopsy method for which sufficient numbers of cells were obtained will be used for primary analysis.

Table 3 provides an overview of the planned biomarker analyses, with full details of data displays being presented in
Appendix 10: List of Data Displays.

Table 3 Overview of Biomarker Analyses

Endpoint	Absolute							Proportion						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
iLN Biopsies and Peripheral Blood														
Leukocyte subsets	Y		Y	Y	Y		Y	Y		Y	Y	Y		Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- 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.

7.1.1.1. Interim Analyses 1

The analysis performed at the interim will be a subset of the final analysis as given by Table 4.

Table 4 Overview of Biomarker Analyses for Interim

Endpoint	Absolute							Proportion						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
iLN Biopsy and Peripheral Blood														
Leukocyte Count				Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.

Endpoint	Absolute							Proportion						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L

- 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.

7.1.1.2. Interim Analyses 2

The analysis performed at the interim will be a subset of the final analysis as given by Table 4.

Table 5 Overview of Biomarker Analyses for Interim

Endpoint	Absolute							Proportion						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
iLN Biopsy and Peripheral Blood														
Leukocyte Count				Y			Y	Y	Y		Y	Y		Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- 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.

7.1.2. Planned Biomarker Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Proportion of flow cytometry cell counts
Model Specification
• Endpoints analyzed for each flow cytometry cell type using generalized linear mixed models (GLMM). • The analysis will be performed on the parameters listed in Appendix 8: Biomarker Analyses • Terms in GLMM model will include: Fixed categorical: group, sample type, and the interaction of group with sample type Random effect: subject Where group is either HV or NOT1D, and sample type is peripheral blood, core biopsy or fine needle aspirate.
Model Checking & Diagnostics
• Refer to Appendix 7: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• For proportional cell counts, these models will estimate the mean (or geometric) cell count for each sample type in each group, comparing means using ratios as outlined in the primary hypothesis section.

8. SECONDARY STATISTICAL ANALYSES

8.1. Biomarker Analyses

8.1.1. Overview of Planned Biomarker Analyses

As per Primary Analysis, see Section 7.1.2, but for secondary comparisons detailed in Figure 1.

8.2. Safety Analyses

8.2.1. Overview of Planned Adverse Event Analyses

The safety 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 10: List of Data Displays.

Table 6 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC	Y		Y
Common AEs by Overall Frequency	Y		
Common Grade 2-4 AEs by Overall Frequency	Y		
Subjects & No. of Occurrences of Common Non-Serious AEs by SOC and PT	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT & Verbatim Text			Y
Serious and Other Significant AEs			
Fatal Serious AEs	Y		Y
Non-Fatal Serious AEs			Y
Serious AEs by SOC	Y		
Reasons for Considering as a Serious AE			Y
AEs Leading to Withdrawal from Study by Overall Frequency	Y		Y
Subjects and Number of Occurrences of Serious and Fatal Serious AEs	Y		

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, 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.

8.2.2. Overview of Planned Other Safety Analyses

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

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in
Appendix 10: List of Data Displays.

Table 7 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Laboratory Values						
Haematology			Y			
Clinical Chemistry			Y			
Urinalysis			Y			
Other Screening Tests			Y			
Vital Signs						
Vitals Findings	Y		Y	Y		Y
Vitals Values (PCI)	Y		Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- 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.

8.2.3. Interim Analysis 1

No formal safety analyses will be produced for the interim analysis.

8.2.4. Interim Analysis 2

No formal safety analyses will be produced for the interim analysis.

9. REFERENCES

GlaxoSmithKline Document Number 2015N246275_03 (2017-MAR-06 Amendment No. 3): Exploration of the peripheral immune system in subjects with New Onset T1 Diabetes (NOT1D)

10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 10.2	Appendix 2: Time & Events
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Biomarkers
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance
Section 10.7	Appendix 7: Model Checking and Diagnostics for Statistical Analyses
Section 10.8	Appendix 8: Biomarker Analyses
Other RAP Appendices	
Section 10.9	Appendix 9: Abbreviations & Trade Marks
Section 10.10	Appendix 10: List of Data Displays
Section 10.11	Appendix 11: Example Mock Shells for Data Displays

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

10.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Eligibility criteria not met
02	Excluded medication, vaccine or device
03	Equipment procedures
04	Biological sample specimen procedures

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Screening procedures in addition to those listed below are (outpatient visit): Informed consent; Inclusion / Exclusion criteria; demography.

Procedure	Screening (between -42 to 7 days prior to study session)	Study Session Day 1			Telephone follow-up Day ~2 to ~ Day 4	Telephone follow-up Day ~7 to Day ~14	Notes
		Pre biopsy	Biopsy	End of study session visit			
Full physical exam	X						To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Medical history / Past and current medical conditions	X						To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Laboratory assessments (see Section 6.7.5)	X						To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Concomitant medication review	X	X			X	X	
Alcohol Urine Test and Test for Drugs of Abuse	X	X					

Procedure	Screening (between -42 to 7 days prior to study session)	Study Session Day 1			Telephone follow-up Day ~2 to ~ Day 4	Telephone follow-up Day ~7 to Day ~14	Notes
		Pre biopsy	Biopsy	End of study session visit			
Urine Pregnancy test (in women of child bearing potential)	X	X					
Vital signs	X	X		X			To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Medical history / Past and current medical conditions		X					
Proposed biopsy site review		X					
Peripheral blood collection for cell isolation and metabonomics analyses		X					
Peripheral blood collection for genetics		X					

Procedure	Screening (between -42 to 7 days prior to study session)	Study Session Day 1			Telephone follow-up Day ~2 to ~ Day 4	Telephone follow-up Day ~7 to Day ~14	Notes
		Pre biopsy	Biopsy	End of study session visit			
Peripheral blood collection for haematology, clinical chemistry only, (see Section 6.7.5)		X					To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Inguinal lymph node biopsy (fine needle aspirate & core biopsy)			X				
Wound assessment				X	X (telephone)	X (telephone)	To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Pre- & post-biopsy questionnaire to assess subject experience of lymph node biopsy		X			X (via telephone: questionnaire to be filled in on the day after the procedure)		

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	No Treatment	No Treatment	1

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Study Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
1	Healthy Volunteers	Healthy Volunteers	1
2	NOT1D	NOT1D	2

10.3.2. Baseline Definition & Derivations

10.3.2.1. Baseline Definitions

For all endpoints the baseline value will be the latest pre-biopsy assessment.

10.3.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	=Post-Biopsy Value – Baseline
% Change from Baseline	=100 x [(Post-Biopsy Value – Baseline) / Baseline]

10.3.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used to perform all data analyses and generation of displays.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: \\arprod\nocompound\mid203158\[reporting effort] \\arwork\nocompound\mid203158\[reporting effort]
QC Spreadsheet	: \\arprod\nocompound\mid203158\[reporting effort]\qc
Analysis Datasets	

Reporting Process
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.
Generation of RTF Files
• RTF files will be generated for the final analysis only.

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 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. o RTF files will be generated for displays	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses : • Planned time will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • 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: • Planned and actual time will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • 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.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

10.4. Appendix 4: Derived and Transformed Data

10.4.1. 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. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

10.4.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

10.4.3. Safety

Laboratory Parameters

• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  o Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  o Example 3: 0 Significant Digits = '< x' becomes x – 1

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined one who has completed all phases of the study including the follow-up call(s).The end of the study is defined as the last subject's last telephone call As defined in the protocol the overall study duration for each subject will be up to 8 weeks, including the screening period. • Withdrawn subjects may be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in displays, unless otherwise specified.

10.5.2. 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.

10.5.2.1. Handling of Missing Dates

Completely missing dates will remain missing, with no imputation applied

10.5.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• 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. • The recorded partial date will be displayed in listings.
Adverse Events	• 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 Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. ○ The AE will then be considered to start on-treatment (worst 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. • The recorded partial date will be displayed in listings.

10.5.2.3. Handling of Missing Data for Statistical Analysis

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

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. 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
While 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	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.6.2. 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

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
Diastolic Blood Pressure	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
Heart Rate	bpm	≥ 15	≥ 30	≥ 15	≥ 30

10.7. Appendix 7: Model Checking and Diagnostics for Statistical Analyses

10.7.1. Statistical Analysis Assumptions

Endpoint(s)	• Proportion of flow cytometry cell counts
Analysis	• GLMM

- Model assumptions will be applied, but appropriate adjustments maybe applied based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the RANDOM line.
  - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- 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.

10.8. Appendix 8: Biomarker Analyses

10.8.1. Frequency of Leukocytes

Test Analyte	Details
Core biopsy total cell number	Total number of cells obtained from pooled core biopsies
Fine Needle Aspirate total cell number	Total number of cells obtained from pooled fine needle aspirates

10.8.2. Frequency and phenotype of leukocyte subsets by flow cytometry

10.8.2.1. B_DC_Monocyte Panel

Test Analyte	Details
%DC (MNC)	NONCD16hiCD3-CD19-HLADR+CD14-CD16-
%Myeloid DC (DC)	NONCD16hiCD3-CD19-CD14-CD16-HLADR+CD11C+CD123-
%pDC (DC)	NONCD16hiCD3-CD19-CD14-CD16-HLADR+CD11C-CD123+
%Plasmablast (B)	NONCD16hiCD19+CD27+CD38+
%Circulating B (B)	NONCD16hiCD19+Plasmablast-CD27+IgD+
%Classical B (B)	NONCD16hiCD19+Plasmablast-CD27+IgD-
%Double neg B (B)	NONCD16hiCD19+Plasmablast-CD27-IgD-
%Naïve B (B)	NONCD16hiCD19+Plasmablast-CD27-IgD+
%Transitional B (B)	NONCD16hiCD19+Plasmablas-CD27-IgD+CD38+CD24+
%CD56bright NK (NK)	NONCD16hiCD3-CD19-CD14-CD16-CD56hi
%CD56loCD16+ NK (NK)	NONCD16hiCD3-CD19-CD14-CD56loCD16+
%CD56loCD16- NK (NK)	NONCD16hiCD3-CD19-CD14-CD56loCD16-
%CD14+ monocyte (monocyte)	NONCD16hiCD3-CD19-NK-HLADR+Monocyte+CD14+
%CD14+CD16+ monocyte (monocyte)	NONCD16hiCD3-CD19-NK-HLADR+Monocyte+CD14+CD16+
%CD16+ monocyte (monocyte)	NONCD16hiCD3-CD19-NK-HLADR+Monocyte+CD16+

10.8.2.2. T Cell panel

Test Analyte	Details
%CD8 Tn (CD8)	CD3+CD4-CD45RA+CCR7+CD95-
%CD8 Tcm (CD8)	CD3+CD4-CD45RA-CCR7+
%CD8 Tem (CD8)	CD3+CD4-CD45RA-CCR7-
%CD8 Temra (CD8)	CD3+CD4-CD45RA+CCR7-
%CD8 Tscm (CD8)	CD3+CD4-CD45RA+CCR7+CD95+
%Tconv Tn (Tconv)	CD4+Treg-CD45RA+CCR7+CD95-
%Tconv Tcm (Tconv)	CD4+Treg-CD45RA-CCR7+
%Tconv Tem (Tconv)	CD4+Treg-CD45RA-CCR7-
%Tconv Temra (Tconv)	CD4+Treg-CD45RA+CCR7-

Test Analyte	Details
%Tconv Tscm (Tconv)	CD4+Treg-CD45RA+CCR7+CD95+
%Tconv Th1 (mTconv)	CD4+Treg-CXCR5-CXCR3+CCR10-CCR6-
%Tconv Th1Th17 (mTconv)	CD4+Treg-CXCR5-CXCR3+CCR10-CCR6+
%Tconv Th17 (mTconv)	CD4+Treg-CXCR5-CXCR3-CCR4+CCR10-CCR6+
%Tconv Th2 (mTconv)	CD4+Treg-CXCR5-CXCR3-CCR4+CCR10-CCR6-
%Tconv Th22 (mTconv)	CD4+Treg-CXCR5-CXCR3-CCR4+CCR10+CCR6+
%Tconv Tfh (mTconv)	CD4+Treg-CXCR5+
%Tconv PD-1+ ICOS+ Tfh (mTconv)	CD4+Treg-CXCR5+PD-1+ICOS+
%Treg Th1 (mTreg)	CD4+CD25+CD127loCXCR5-CXCR3+CCR10-CCR6-
%Treg Th1Th17 (mTreg)	CD4+CD25+CD127loCXCR5-CXCR3+CCR10-CCR6+
%Treg Th17 (mTreg)	CD4+CD25+CD127loCXCR5-CXCR3-CCR4+CCR10-CCR6+
%Treg Th2 (mTreg)	CD4+CD25+CD127loCXCR5-CXCR3-CCR4+CCR10-CCR6-
%Treg Th22 (mTreg)	CD4+CD25+CD127loCXCR5-CXCR3-CCR4+CCR10+CCR6+
%Treg Tfh (mTreg)	CD4+CD25+CD127loCXCR5+
%Treg PD-1+ ICOS+ Tfh (mTreg)	CD4+CD25+CD127loCXCR5+PD-1+ICOS+

10.8.2.3. Treg panel

Test Analyte	Details
%CD15s+ Tconv (Tconv)	CD3+CD4+CD25-FOXP3-CD15S+
%CD69+ Tconv (Tconv)	CD3+CD4+CD25-FOXP3-CD69+
%Helios+ Tconv (Tconv)	CD3+CD4+CD25-FOXP3-HELIOS+
%Ki67+ Tconv (Tconv)	CD3+CD4+CD25-FOXP3-KI67+
%CD15s+ mTconv (mTconv)	CD3+CD4+CD25-FOXP3-CD45RA-CD15S+
%CD69+ mTconv (mTconv)	CD3+CD4+CD25-FOXP3-CD45RA-CD69+
%Helios+ mTconv (mTconv)	CD3+CD4+CD25-FOXP3-CD45RA-HELIOS+
%Ki67+ mTconv (mTconv)	CD3+CD4+CD25-FOXP3-CD45RA-KI67+
%Treg (CD4)	CD3+CD4+CD25+FOXP3+
%aTreg (Treg)	CD3+CD4+CD25+FOXP3+CD45RA-
%mTreg (Treg)	CD3+CD4+CD25+FOXP3medCD54RA-
%rTreg (Treg)	CD3+CD4+CD25+FOXP3medCD45RA+
%CD15s+ Treg (Treg)	CD3+CD4+CD25+FOXP3+CD15S+
%CD69+ Treg (Treg)	CD3+CD4+CD25+FOXP3+CD69+
%Helios+ Treg (Treg)	CD3+CD4+CD25+FOXP3+HELIOS+
%Ki67+ Treg (Treg)	CD3+CD4+CD25+FOXP3+KI67+
%CD69+ CD8 (CD8)	CD3+CD8+CD69+
%Ki67+ CD8 (CD8)	CD3+CD8+KI67+

10.8.2.4. Suppressive activity of regulatory cells

Test Analyte	Details
Percentage suppression 0:1	Treg: Tconventional cell ratio 0:1
Percentage suppression 1:2	Treg: Tconventional cell ratio 1:2
Percentage suppression 1:4	Treg: Tconventional cell ratio 1:4

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
BL	Baseline
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FNA	Fine needle aspirate
HV	Healthy volunteer
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
iLN	Inguinal lymph node
IMMS	International Modules Management System
GLMM	Generalized linear mixed model
GUI	Guidance
GSK	GlaxoSmithKline
NOT1D	New Onset Type 1 Diabetes Mellitus
PBMC	Peripheral blood mononuclear cell
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SOC	System Organ Class
TCR / BCR	T-cell Receptor / B-cell Receptor
TFL	Tables, Figures & Listings

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.nn	1.01 to 1.nn
Safety	2.01 to 2.nn	2.01 to 2.nn
Pharmacodynamic and / or Biomarker	3.01 to 3.nn	3.01 to 3.nn
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacodynamic and / or 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.'

10.10.3. Deliverable [Priority]

Delivery	Description
IA SAC	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

10.10.4. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Frequency and phenotype of leukocyte subsets by flow cytometry					
3.1.	Safety	PD_T1	Summary of B_DC_Monocyte Panel by Method and Patient Group	Parameters listed in Section 10.8.2.1	IA SAC
3.2.	Safety	PD_T2	Statistical Analyses of B_DC_Monocyte Panel by Method and Patient Group	Parameters listed in Section 10.8.2.1	IA SAC
3.3.	Safety	PD_T1	Summary of T Cell Panel by Method and Patient Group	Parameters listed in Section 10.8.2.2	IA SAC
3.4.	Safety	PD_T2	Statistical Analyses of T Cell Panel by Method and Patient Group	Parameters listed in Section 10.8.2.2	IA SAC
3.5.	Safety	PD_T1	Summary of Treg Panel by Method and Patient Group	Parameters listed in Section 10.8.2.3	IA SAC
3.6.	Safety	PD_T2	Statistical Analyses of Treg Panel by Method and Patient Group	Parameters listed in Section 10.8.2.3	IA SAC
Suppressive activity of regulatory cells					
3.7.	Safety	PD_T1	Summary of Suppressive activity of regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.4	IA SAC
3.8.	Safety	PD_T2	Statistical Analyses of Suppressive activity of regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.4	IA SAC

10.10.5. Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Frequency and phenotype of leukocyte subsets by flow cytometry					
3.1.	Safety	PD_F1	Boxplots of B_DC_Monocyte Panel by Method and Patient Group	Parameters listed in Section 10.8.2.1	IA SAC
3.2.	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of B_DC_Monocyte Panel	Parameters listed in Section 10.8.2.1	IA SAC
3.3.	Safety	PD_F1	Boxplots of T Cell Panel by Method and Patient Group	Parameters listed in Section 10.8.2.2	IA SAC
3.4.	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of T Cell Panel	Parameters listed in Section 10.8.2.1	IA SAC
3.5.	Safety	PD_F1	Boxplots of Treg Panel by Method and Patient Group	Parameters listed in Section 10.8.2.3	IA SAC
3.6.	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of Treg Panel	Parameters listed in Section 10.8.2.1	IA SAC
Suppressive activity of regulatory cells					
3.7.	Safety	PD_F1	Boxplots of Suppressive activity of regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.4	IA SAC
3.8.	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of Suppressive activity of regulatory cells	Parameters listed in Section 10.8.2.1	IA SAC

10.10.6. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Frequency and phenotype of leukocyte subsets by flow cytometry					
1.	Safety	PD_L1	Listing of B_DC_Monocyte Panel by Biomarker	Parameters listed in Section 10.8.2.1	IA SAC
2.	Safety	PD_L2	Listing of B_DC_Monocyte Panel by Group and Subject ID	Parameters listed in Section 10.8.2.1	IA SAC
3.	Safety	PD_L1	Listing of T Cell Panel by Biomarker	Parameters listed in Section 10.8.2.2	IA SAC
4.	Safety	PD_L2	Listing of T Cell Panel by Group and Subject ID	Parameters listed in Section 10.8.2.2	IA SAC
5.	Safety	PD_L1	Listing of Treg Panel by Biomarker	Parameters listed in Section 10.8.2.3	IA SAC
6.	Safety	PD_L2	Listing of Treg Panel by Group and Subject ID	Parameters listed in Section 10.8.2.3	IA SAC
Suppressive activity of regulatory cells					
7.	Safety	PD_L1	Listing of Suppressive activity of regulatory cells by Biomarker	Parameters listed in Section 10.8.2.4	IA SAC
8.	Safety	PD_L2	Listing of Suppressive activity of regulatory cells by Group and Subject ID	Parameters listed in Section 10.8.2.4	IA SAC

10.11. Appendix 11: Example Mock Shells for Data Displays

Example: PD_T1

Protocol: OTX203158 Page 1 of X
Population: Safety

Table X.X
Summary of XXXXX by Method and Patient Group

Subset: XXXXXXXXX (Unit)

			Method		
Group	N	Statistic	Blood	FNA	Core
HV	XX	n	XX	XX	XX
		Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
		95% CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
		Min	X.X	X.X	X.X
		Median	X.XX	X.XX	X.XX
		Max	X.X	X.X	X.X
NOT1D	XX	n	XX	XX	XX
		Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
		95% CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
		Min	X.X	X.X	X.X
		Median	X.XX	X.XX	X.XX
		Max	X.X	X.X	X.X

Note: n is the number of subjects with evaluable data for the specific biopsy.
userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_T2 – Page 1

Protocol: OTX203158
Population: Safety

Table X.X
Statistical Analyses of XXXXX by Method and Patient Group

Subset: XXXXXXXXX (Unit)

Method	Statistic	Group HV (N=XX)	Group NOT1D (N=XX)	Difference
Blood	n	XX	XX	
	LS Mean (SE)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95% CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
iLN	n	XX	XX	
	LS Mean (SE)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95% CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
FNA	n	XX	XX	
	LS Mean (SE)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95% CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
Core	n	XX	XX	
	LS Mean (SE)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95% CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX

Note: n is the number of subjects with evaluable data for the specific biopsy. Only subjects with data for both pairs of methods will be used in the comparisons. Model used…

userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_T2 – Page 2

Protocol: OTX203158
Population: Safety

Table X.X
Statistical Analyses of XXXXX by Method and Patient Group

Subset: XXXXXXXXX (Unit)

Comparison	Statistic	Group HV (N=XX)	Group NOT1D (N=XX)
iLN vs Blood	n	XX	XX
	LS Mean (SE) - iLN	X.XX (X.XXX)	X.XX (X.XXX)
	LS Mean (SE) - Blood	X.XX (X.XXX)	X.XX (X.XXX)
	LS Mean Ratio (95% CI)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)
FNA vs Blood	n	XX	XX
	LS Mean (SE) - iLN	X.XX (X.XXX)	X.XX (X.XXX)
	LS Mean (SE) - Blood	X.XX (X.XXX)	X.XX (X.XXX)
	LS Mean Ratio (95% CI)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)

.. ..
Continue for
Core vs Blood

FNA vs Core

Note: n is the number of subjects with evaluable data for the specific biopsy. Only subjects with data for both pairs of methods will be used in the comparisons. Model used…

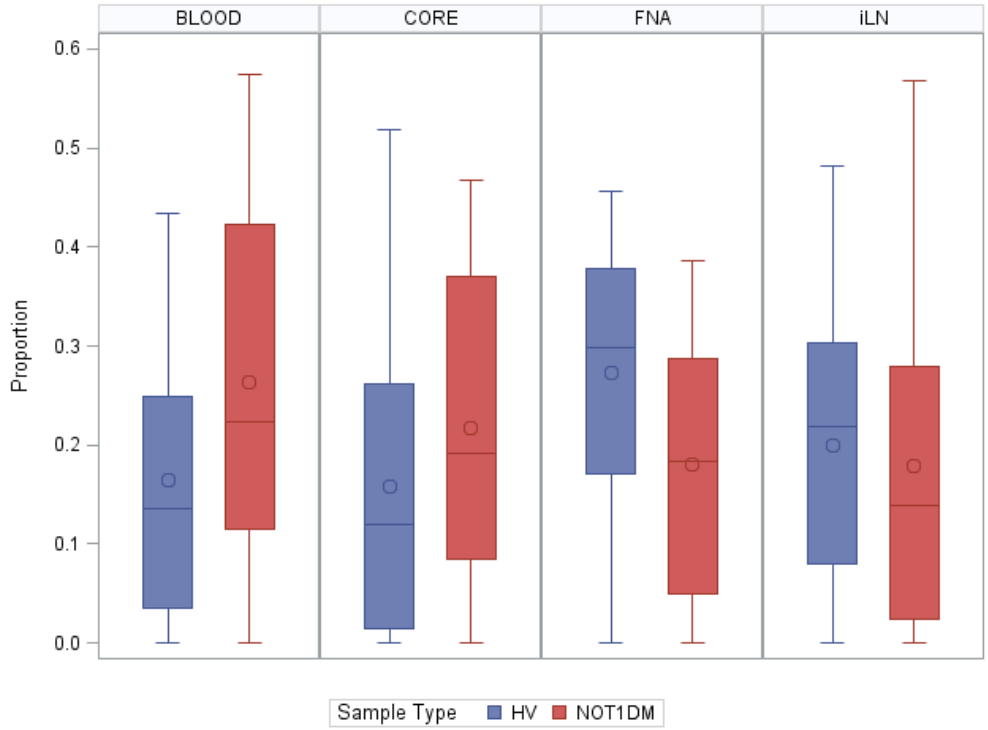
userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_F1

Protocol: OTX203158
Population: Safety

Figure X.X
Boxplots of XXXXX by Method and Patient Group

Biomarker: XXXXXXXXX (Unit)



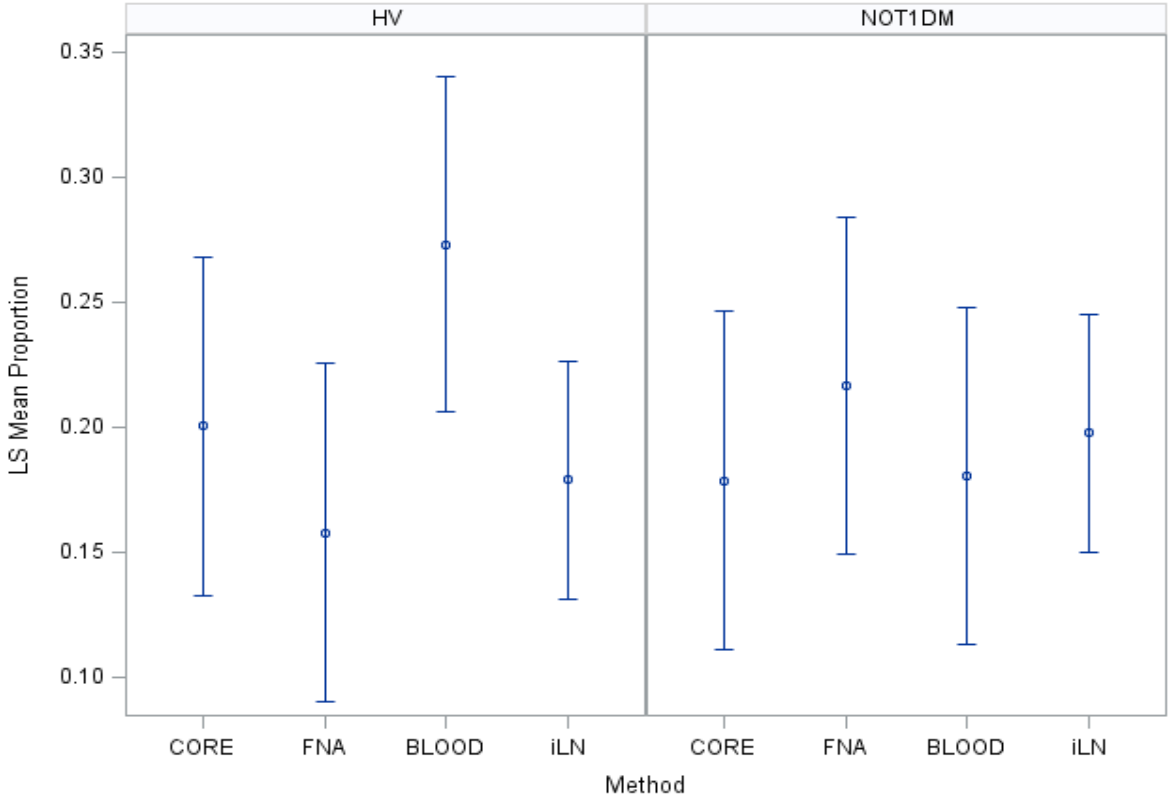
userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_F2 – Page 1

Protocol: OTX203158
Population: Safety

Figure X.X
LS Mean Estimates and Differences with 95% CI of XXXXX

Biomarker: XXXXXXXXX (Unit)



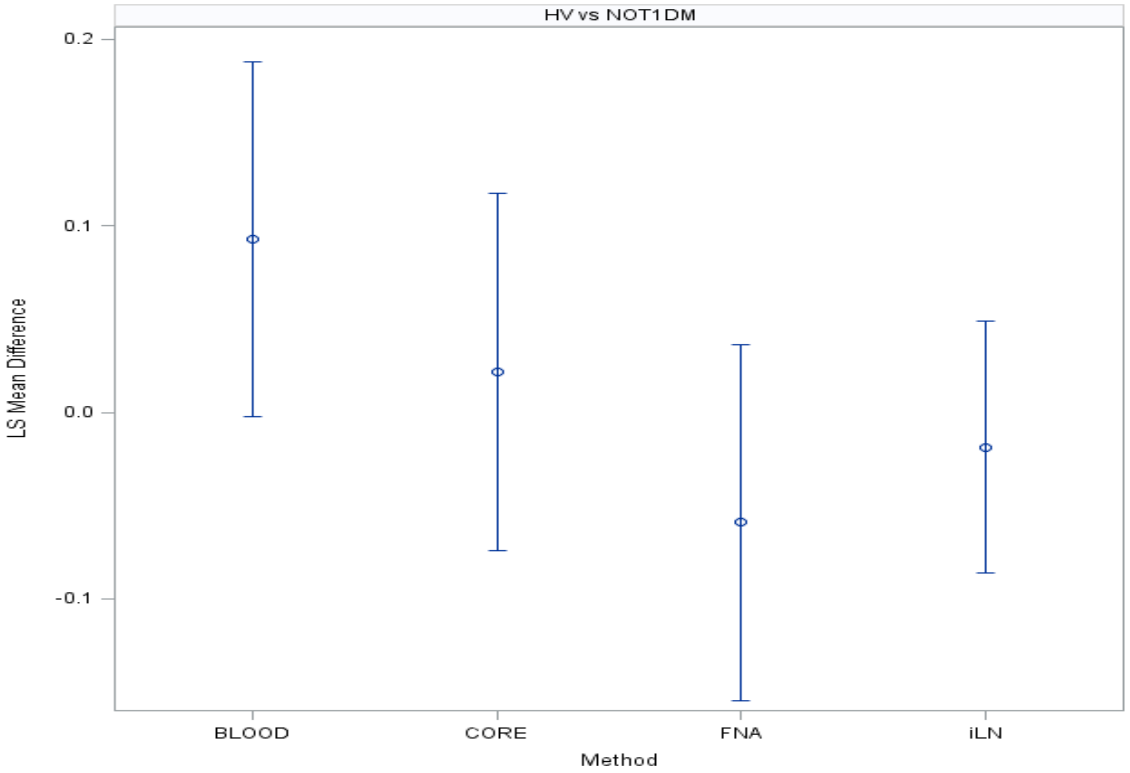
userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_F2 – Page 2

Protocol: OTX203158
Population: Safety

Figure X.X
LS Mean Estimates and Differences with 95% CI of XXXXX

Biomarker: XXXXXXXXX (Unit)



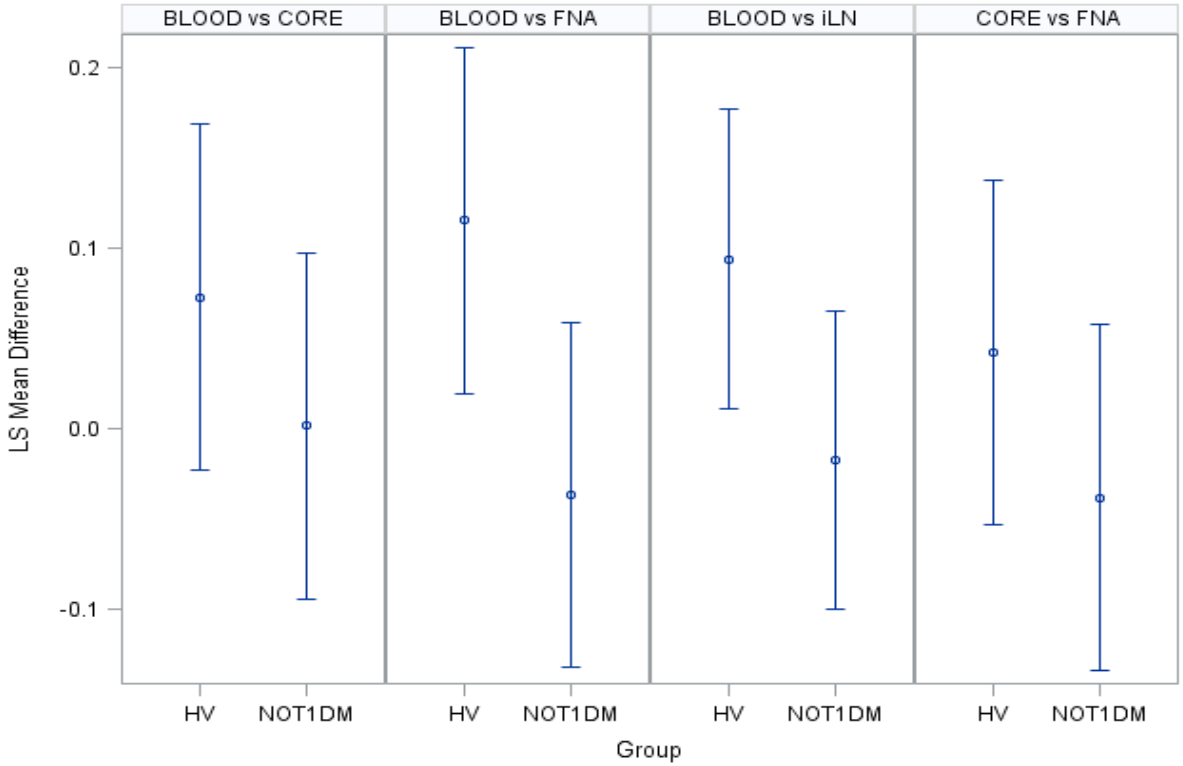
userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_F2 – Page 3

Protocol: OTX203158
Population: Safety

Figure X.X
LS Mean Estimates and Differences with 95% CI of XXXXX

Biomarker: XXXXXXXXX (Unit)



userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_L1

Protocol: OTX203158
Population: Safety

Listing X
Listing of XXXXX by Biomarker

Biomarker: XXXXXXXXX (Unit)

Group	Subject ID/Age/Sex/Race	Method		
		Blood	FNA	Core
HV	PPD/XX/X/XXXXXXX	X.X		
	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
NOT1D	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
	/XX/X/XXXXXXX			
	…			

userid: filelocation\filename.sas ddMMMyyyy hh:mm

Example: PD_L2

Protocol: OTX203158
Population: Safety

Listing X
Listing of XXXXX by Group and Subject ID

Group/Subject ID/Age/Sex/Race: HV PPD /XX/X/XXXXXXX

Biomarker	Method		
	Blood	FNA	Core
Biomarker 1	X.X	X.X	X.X
Biomarker 2	X.X	X.X	X.X
Biomarker 3	X.X	X.X	X.X
Biomarker 4	X.X	X.X	X.X
…			

userid: filelocation\filename.sas ddMMMyyyy hh:mm

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

Title	:	Reporting and Analysis Plan for Exploration of the peripheral immune system in subjects with New Onset T1 Diabetes (NOT1D)
Compound Number	:	None
Effective Date	:	15-JAN-2018

Description :

- The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and outputs for the final analyses.

RAP Author(s):

PPD
Statistics Leader (II Clinical Statistics)

RAP Team Approvals:

Approver	Date	Approval Method
PPD Principal Programmer (II Clinical Programming)	12-JAN-2018	PharmaTMF
PPD Scientific leader (II DPU Mechanistic Medicine Discovery)	15-JAN-2018	Email
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PPD Data Quality Leader (II Clinical Pharmacology Science and Study Operations)	12-JAN-2018	PharmaTMF
PPD Principal Clinical Research Scientist (II Clinical Pharmacology Science and Study Operations)	12-JAN-2018	PharmaTMF

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
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PPD Job Title (II Clinical Programming)	12-JAN-2018	PharmaTMF

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 203158:

Revision Chronology:		
2015N246275_00	11-Dec-2015	Original
2015N246275_01	04-Apr-2016	Changes to the exploratory objectives, removal of LN Questionnaire, plus clarifications and corrections.
2015N246275_02	06-Oct-2016	Corrections to Time & Events Table and screening tests
2015N246275_03	06-Mar-2017	Updated text around interim analyses, change to inclusion criteria and clarifications.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

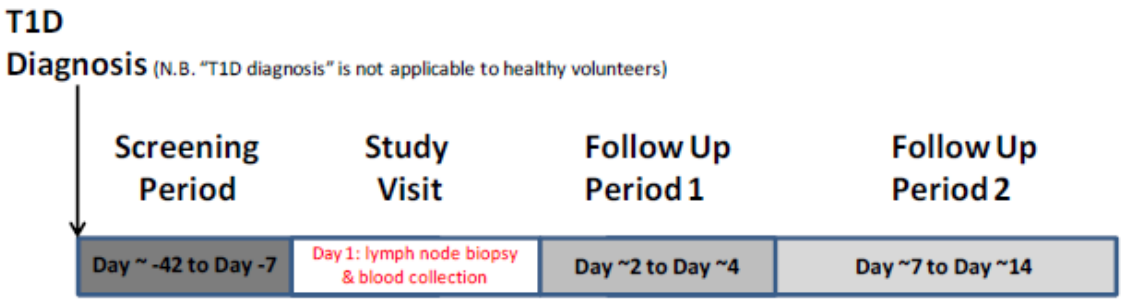
Exploratory objectives 2-5 were not evaluated due to only a limited number of cells being available to analyze, as no data has been collected these have been removed from the RAP, except for Section 2 to maintain consistency with the protocol.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
1) To assess the frequency and phenotype of leukocyte subsets in iLN and peripheral blood in HVs and NOT1D subjects	• Absolute number and/or proportion of leukocyte subsets in iLN and peripheral blood
Secondary Objectives	**Secondary Endpoints**
1) To assess the frequency and phenotype of leukocyte subsets in iLN core biopsies and iLN fine needle aspirates in HVs and NOT1D subjects	• Absolute number and/or proportion of leukocyte subsets in iLN core biopsies and iLN fine needle aspirates
2) To assess the safety and tolerability of iLN biopsy as well as expectations and experience of the biopsy procedure	• Number of AEs and SAEs following lymph node biopsy procedure • Descriptive data obtained by a questionnaire on the acceptability of iLN biopsy in research setting.
Exploratory Objectives*	**Exploratory Endpoints**
1) To assess suppression activity of T regulatory lymphocytes from the iLN and peripheral blood in HVs and NOT1D subjects	• Relative levels of T lymphocyte suppressive activity of cells from iLN and peripheral blood respectively
2) To assess the frequency of cytokine-producing lymphocytes in HVs and NOT1D subjects	• Proportion of lymphocyte populations producing pro-inflammatory and/or anti-inflammatory cytokines in iLN and peripheral blood
3) To assess clonal expansion of T and B lymphocyte populations in HVs and NOT1D subjects	• Comparison of TCR and BCR usage in lymphocytes in iLN and peripheral blood
4) To assess the gene expression fingerprint of auto-antigen specific lymphocytes in HVs and NOT1D subjects	• Gene expression levels of sorted auto antigen stimulated T lymphocyte populations in iLN and peripheral blood
5) To assess the phenotype and transcriptomic fingerprint of stromal cells from iLN core biopsy samples in HVs and NOT1D subjects	• Absolute number and/or proportion of stromal cell subsets and gene expression levels of stromal cell subsets from iLN core biopsy samples

* The Exploratory objectives / endpoints are listed in order of priority and the conduct of any experimental assays will be dependent on the material available (i.e. number of cells obtained) from iLN biopsies and peripheral blood.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	A multi-centre, non-drug treatment study to compare differences in immune cells derived from iLN and peripheral blood of NOT1D subjects and HVs.
Dosing	• Not applicable (non-drug interventional study)
Treatment Assignment	• Not applicable
Interim Analysis	Interim analyses will be carried out at the following timepoints: • After at least 5 HVs have been biopsied. • An interim analysis will be carried out after the recruitment of 5 evaluable HVs and 5 evaluable NOT1D subjects. These are further described in Section 3.1.

2.4. Statistical Hypotheses

This study is designed to explore the phenotype of immune cells in the iLN and peripheral blood (such as, but not restricted to PBMCs) of NOT1D subjects compared to HVs.

There are no formal hypotheses being tested due to the exploratory nature of the study. Primary comparisons of NOT1D subjects to HVs will be made using an estimation approach, providing point estimates and confidence intervals.

Secondary comparisons of biopsy methods will be made within NOT1D subjects and HVs using an estimation approach:

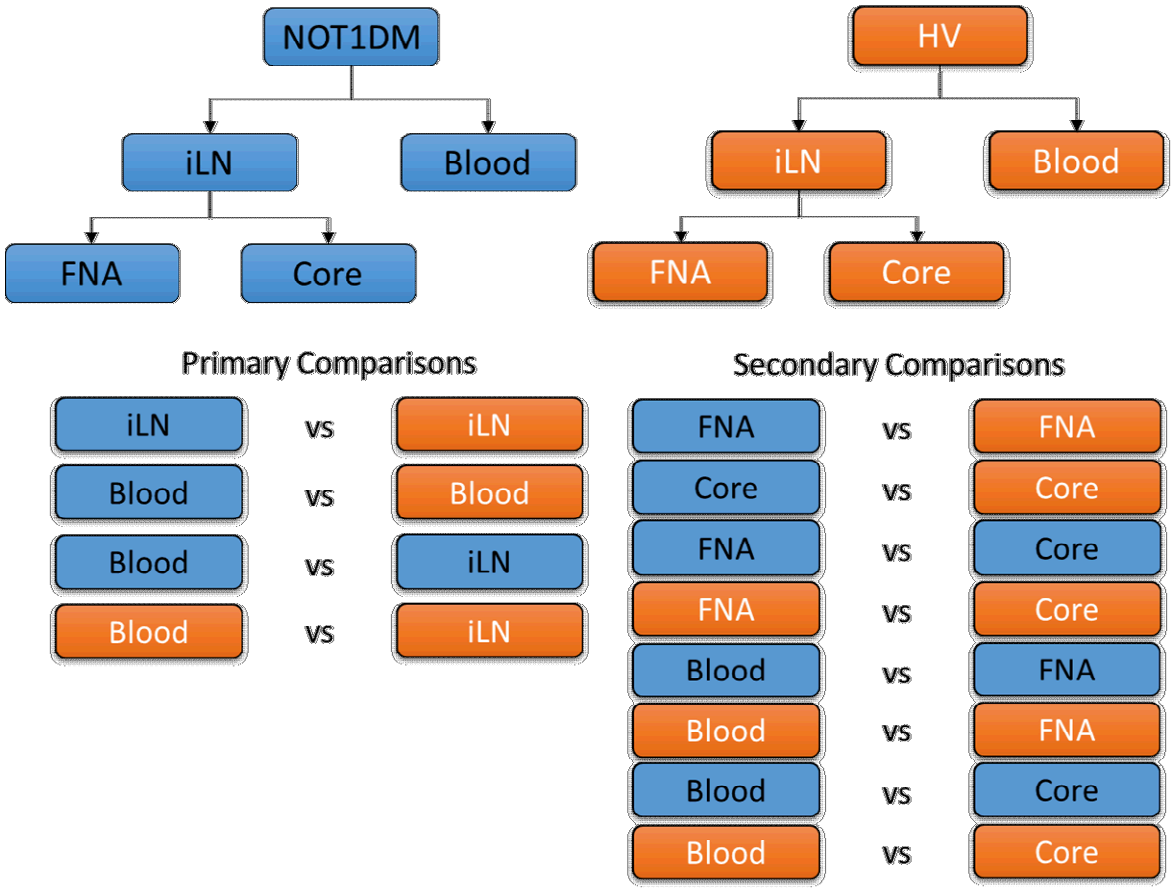
- iLN biopsies will be carried out by two related methods, fine-needle aspirate (FNA) and core biopsy sampling:
- If sufficient numbers of cells to meet the cell number requirements of the primary endpoint are obtained by both biopsy methods, the primary endpoint analysis will be carried out independently for each biopsy method, otherwise only the biopsy

method for which sufficient numbers of cells were obtained will be used for primary analysis.

- If no meaningful differences between biopsy methods are observed, material from both biopsy methods may be pooled to meet exploratory objectives 1, 2, 3 and 4. Material from fine-needle aspirate and core biopsies will not be pooled unless supported by the comparison described above.
- If meaningful differences in the proportion of leukocyte subsets between cells derived from each biopsy method are observed, then:
    - If sufficient number of core biopsy derived cells are available, these will be analysed for exploratory objectives 1 and 2.
    - Fine needle aspirate derived cells will be used to meet exploratory objectives 3 and 4. If insufficient number of core biopsy derived cells are available to meet exploratory objectives 1 and 2, then fine needle aspirate derived cells may be used to meet either or both of those exploratory objectives.

A graphical representation of the comparisons are shown in Figure 1.

Figure 1 - Graphical representation of comparisons



3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Interim Analysis 1

A data look will be carried after the recruitment of a cohort of up to 5 HVs to determine if the quality and quantity of cells derived from either fine needle aspirate or core biopsy of the inguinal lymph node and from peripheral blood are likely to be sufficient to continue the study to meet its primary objective.

The decision rules for the study to continue are:

- Peripheral blood yields > $1x10e^6$ cells, and
- Yield from either iLN biopsy samples > $1x10e^6$ cells.

In addition, the data from the interim analysis will be used to explore the assumptions and feasibility of the primary statistical analysis, and may also be used for pre-programming of outputs for the final analysis.

If the decision is taken to stop the study at the interim, the full safety outputs plus listings of other collected data will be produced.

3.1.2. Interim Analysis 2

An interim analysis will be carried out after the recruitment of 5 evaluable HVs and 5 evaluable NOT1D subjects. The primary purpose of this interim analysis will be to facilitate decision making and study design for a potential follow-up interventional study.

In addition, the interim analysis results would also help to enable prioritization of the exploratory assays and to facilitate the final RAP. Due to uncertainty around variability and precision, the primary analyses described in Section 7 will be performed in order to re-assess the precision of estimates for the comparisons of interest.

3.2. Final Analyses

The final planned primary 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	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who passed screening and entered the study	• Study Population
Safety	• Comprised of all subjects who complete any study assessment	• Study Population • Safety
Core Biopsy	• Subjects in the 'Safety' population for whom at least one lymph node core biopsy was taken	• Biomarker
Fine needle aspirate Biopsy	• Subjects in the 'Safety' population for whom at least one lymph node fine needle aspirate biopsy was taken	• Biomarker
Biopsy	• Subjects in both 'Core Biopsy' and 'fine needle aspirate biopsy' populations	• Biomarker
Blood	• Subjects in the 'Safety' population for whom one blood sample was taken for analysis of cells derived from peripheral blood.	• Biomarker
Per Protocol	• Subjects in the 'Safety' Population who were compliant with the Protocol	• Biomarker

NOTES :

- Please refer to Appendix 10: List of Data Displays which details the population to be used for each displays 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 summarised and listed.
- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).
    - 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 summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.
- Analyses may be repeated on the Per Protocol population if deemed important.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	No Treatment	No Treatment	n/a

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Study Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
1	Healthy Volunteers	Healthy Volunteers	1
2	NOT1D	NOT1D	2

5.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-biopsy assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to biopsy and used as baseline.

5.3. Change from Baseline Definitions

Definition	Reporting Details
Change from Baseline	=Post-Biopsy Value – Baseline
% Change from Baseline	=100 x [(Post-Biopsy Value – Baseline) / Baseline]

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates may be used in descriptive summaries and statistical analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Covariates	Age, Gender, Site

NOTES:

- The effect of Age/Gender will be explored if it was not possible to match all subjects by age and gender.
- The effect of site will be explored

5.4.2. Examination of Subgroups

No planned subgroups will be examined.

5.5. Multicentre Studies

There are no planned adjustments made for multiple centres in this study.

5.6. Multiple Comparisons and Multiplicity

There are no planned adjustments for multiple comparisons or multiplicity.

5.7. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Table 1 Overview of Appendices

Section	Component
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Model Checking and Diagnostics for Statistical Analyses
10.8	Appendix 8: Biomarker Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the enrolled population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, will be based on GSK Core Data Standards.

The number and percent of subjects will be reported for the responses for the categorical Pre-Biopsy and Post-Biopsy lymph node questionnaire data. All questions will be listed.

Details of the planned displays are presented in Appendix 10: List of Data Displays

6.1.1. Interim Analysis 1

No study population analyses will be produced for the first interim analysis.

6.1.2. Interim Analysis 2

No study population analyses will be produced for the first interim analysis.

7. PRIMARY STATISTICAL ANALYSES

7.1. Biomarker Analyses

7.1.1. Overview of Planned Biomarker Analyses

The primary biomarker analyses will be based on the 'Safety' population, unless otherwise specified.

Between group (HV vs NOT1D) comparisons will use data from all subjects who have at least one evaluable sample from either method. Between method comparisons and analyses will only be performed in subjects who provide sufficient cells from both methods in each pairwise comparison (as shown in Figure 1).

If sufficient numbers of cells to meet the cell number requirements of the primary endpoint are obtained by both biopsy methods, the primary endpoint analysis will be carried out independently for each biopsy method, otherwise only the biopsy method for which sufficient numbers of cells were obtained will be used for primary analysis.

Details of the planned displays are presented in Appendix 10: List of Data Displays

For biomarkers that indicate a difference between methods or groups, further explanatory analyses may be carried out to explore correlations between biomarkers or the impact of covariates.

7.1.1.1. Interim Analyses 1

Summary statistics and a listing for the overall cell counts will be presented.

7.1.1.2. Interim Analyses 2

All primary and secondary comparisons will be presented, as detailed in Appendix 10: List of Data Displays

7.1.2. Planned Biomarker Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Proportion of flow cytometry cell counts
Model Specification
• Endpoints analyzed for each flow cytometry cell type using generalized linear mixed models (GLMM). The analysis will be performed on the parameters listed in • Appendix 8: Biomarker Analyses • Terms in GLMM model will include: Fixed categorical: group, sample type, and the interaction of group with sample type Random effect: subject Where group is either HV or NOT1D, and sample type is peripheral blood, core biopsy or fine needle aspirate.
Model Checking & Diagnostics
Refer to • Appendix 7: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• For proportional cell counts, these models will estimate the mean (or geometric mean) proportion for each sample type in each group, comparing means using differences or ratios as outlined in the primary hypothesis section.

7.2. Secondary statistical analyses

7.3. Biomarker Analyses

7.3.1. Overview of Planned Biomarker Analyses

As per Primary Analysis, see Section 7.1, but for secondary comparisons detailed in Figure 1.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned

8.3.1. Interim Analysis 1

No formal safety analyses will be produced for the interim analysis.

8.3.2. Interim Analysis 2

No formal safety analyses will be produced for the interim analysis.

9. REFERENCES

GlaxoSmithKline Document Number 2015N246275_03 (2017-MAR-06 Amendment No. 3): Exploration of the peripheral immune system in subjects with New Onset T1 Diabetes (NOT1D)

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

10.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Eligibility criteria not met
02	Excluded medication, vaccine or device
03	Equipment procedures
04	Biological sample specimen procedures

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Time & Events

Screening procedures in addition to those listed below are (outpatient visit): Informed consent; Inclusion / Exclusion criteria; demography.

Procedure	Screening (between -56 to 7 days prior to study session)	Study Session Day 1			Telephone follow-up Day ~2 to ~ Day 4	Telephone follow-up Day ~7 to Day ~14	Notes
		Pre biopsy	Biopsy	End of study session visit			
Full physical exam	X						To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Medical history / Past and current medical conditions	X	X					To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)

Procedure	Screening (between -56 to 7 days prior to study session)	Study Session Day 1			Telephone follow-up Day ~2 to ~ Day 4	Telephone follow-up Day ~7 to Day ~14	Notes
		Pre biopsy	Biopsy	End of study session visit			
Laboratory assessments	X[1]	X[2]					To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator). 1. Blood testing in fasted condition at screening 2. Haematology and clinical chemistry only on Day 1 in a non fasted condition
Concomitant medication review	X	X			X	X	
Alcohol Urine Test and Test for Drugs of Abuse	X	X					
Urine Pregnancy test (in women of child bearing potential)	X	X					

Procedure	Screening (between -56 to 7 days prior to study session)	Study Session Day 1			Telephone follow-up Day ~2 to ~ Day 4	Telephone follow-up Day ~7 to Day ~14	Notes
		Pre biopsy	Biopsy	End of study session visit			
Vital signs	X	X		X			To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)
Proposed biopsy site review		X					
Peripheral blood collection for cell isolation		X					
Peripheral blood collection for genetics		X					Optional in consenting subjects
Inguinal lymph node biopsy (fine needle aspirate & core biopsy)			X				
Wound assessment				X	X (telephone)	X (telephone)	To be completed if a post study visit is required. Attendance to the unit post study sessions only if necessary (at discretion of investigator)

Procedure	**Screening (between -56 to 7 days prior to study session)**	**Study Session Day 1**			**Telephone follow-up Day ~2 to ~ Day 4**	**Telephone follow-up Day ~7 to Day ~14**	**Notes**
		Pre biopsy	**Biopsy**	**End of study session visit**			
Pre- & post-biopsy questionnaire to assess subject experience of lymph node biopsy		X			X (fill in questionnaire on the day after the procedure, communicate answers via telephone a few days after)		
SAE review	←----------→						
AE review		←----------→					

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: \\arprod\nocompound\mid203158 \\arwork\nocompound\mid203158
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for the final analysis tables only.	

10.3.2. Reporting Standards

General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• 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: • Planned time will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • 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: • Planned and actual time will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.

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.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

10.4. Appendix 4: Derived and Transformed Data

10.4.1. 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. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

10.4.2. Study Population

Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing date and month will have this imputed as '30th June'.
  o The date of final screening will be used as the reference for the calculation.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

10.4.3. Safety

Laboratory Parameters

• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, will imputed using the following rules:
  o If value is below limit of quantification, then 0.5*lower limit of quantification will be used
  o If the value is above upper limit of quantification, then the upper limit of quantification will be used.

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who has completed all phases of the study including the follow-up call(s). The end of the study is defined as the last subject's last telephone call. As defined in the protocol the overall study duration for each subject will be up to 8 weeks, including the screening period. • Withdrawn subjects may be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in displays, unless otherwise specified.

10.5.2. 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 using a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the listing. 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.

10.5.2.1. Handling of Missing Dates

Completely missing dates will remain missing, with no imputation applied.

10.5.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• 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. • The recorded partial date will be displayed in listings.

Element	Reporting Detail
Adverse Events	• 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: 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 However, if these results in a date prior to day of biopsy and the event could possibly have occurred post-biopsy from the partial information, then the biopsy date will be assumed to be the start date. o The AE will then be considered to start post-biopsy (worst case). 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. • The recorded partial date will be displayed in listings.

10.5.2.3. Handling of Missing Data for Statistical Analysis

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

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. 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
While 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	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.6.2. 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

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
Diastolic Blood Pressure	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
Heart Rate	bpm	≥ 15	≥ 30	≥ 15	≥ 30

10.7. Appendix 7: Model Checking and Diagnostics for Statistical Analyses

10.7.1. Statistical Analysis Assumptions

Endpoint(s)	• Proportion of flow cytometry cell counts
Analysis	• GLMM

- Model assumptions will be applied, but appropriate adjustments maybe applied based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the RANDOM line.
    - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- 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.

10.8. Appendix 8: Biomarker Analyses

10.8.1. Frequency of Leukocytes

Test Analyte	Details
Core biopsy total cell number	Total number of cells obtained from pooled core biopsies
Fine Needle Aspirate total cell number	Total number of cells obtained from pooled fine needle aspirates

10.8.2. Frequency and phenotype of leukocyte subsets by flow cytometry

10.8.2.1. B_DC_Monocyte Panel

Test Analyte	Details
%DC (MNC)	NONCD16hiCD3-CD19-NK-HLADR+CD14-CD16- out of mono-nuclear cells
%Myeloid DC (DC)	NONCD16hiCD3-CD19-NK- HLADR+CD14-CD16-CD11C+CD123-
%pDC (DC)	NONCD16hiCD3-CD19-NK-HLADR+CD14-CD16-CD11C-CD123+
%Plasmablast (B)	NONCD16hiCD19+CD27+CD38+
%Circulating B (B)	NONCD16hiCD19+Plasmablast-CD27+IgD+
%Classical B (B)	NONCD16hiCD19+Plasmablast-CD27+IgD-
%Double neg B (B)	NONCD16hiCD19+Plasmablast-CD27-IgD-
%Naïve B (B)	NONCD16hiCD19+Plasmablast-CD27-IgD+
%Transitional B (B)	NONCD16hiCD19+Plasmablast-CD27-IgD+CD38+CD24+
%CD56bright NK (NK)	NONCD16hiCD3-CD19- CD14- CD56hi CD16-
%CD56loCD16+ NK (NK)	NONCD16hiCD3-CD19- CD14- CD56lo CD16+
%CD56loCD16- NK (NK)	NONCD16hiCD3-CD19- CD14- CD56lo CD16-
%CD56+CD16+ NK (NK)	NONCD16hiCD3-CD19- CD14- CD56+ CD16+
% NK (MNC)	NONCD16hiCD3-CD19- CD14- out of mono-nuclear cells
%CD56bright NK (MNC)	NONCD16hiCD3-CD19- CD14- CD56h CD16-i out of mono-nuclear cells
%CD56loCD16+ NK (MNC)	NONCD16hiCD3-CD19- CD14- CD56loCD16+ out of mono-nuclear cells
%CD56loCD16- NK (MNC)	NONCD16hiCD3-CD19- CD14- CD56loCD16- out of mono-nuclear cells
%CD56+CD16+ NK (MNC)	NONCD16hiCD3-CD19- CD14- CD56+CD16+ out of mono-nuclear cells
%CD14+ monocyte (monocyte)	NONCD16hiCD3-CD19-NK-HLADR+Monocyte+CD14+
%CD14+CD16+ monocyte (monocyte)	NONCD16hiCD3-CD19-NK-HLADR+Monocyte+CD14+CD16+
%CD16+ monocyte (monocyte)	NONCD16hiCD3-CD19-NK-HLADR+Monocyte+CD16+
%B (MNC)	NONCD16hiCD19+ out of mono-nuclear cells

10.8.2.2. T Cell panel

Test Analyte	Details
%CD8 Tn (CD8)	CD3+CD4-CD45RA+CCR7+CD95-
%CD8 Tcm (CD8)	CD3+CD4-CD45RA-CCR7+
%CD8 Tem (CD8)	CD3+CD4-CD45RA-CCR7-
%CD8 Temra (CD8)	CD3+CD4-CD45RA+CCR7-
%CD8 Tscm (CD8)	CD3+CD4-CD45RA+CCR7+CD95+
%Tconv Tn (Tconv)	CD3+CD4+Treg-CD45RA+CCR7+CD95-
%TconvTcm (Tconv)	CD3+CD4+Treg-CD45RA-CCR7+
%Tconv Tem (Tconv)	CD3+CD4+Treg-CD45RA-CCR7-
%TconvTemra (Tconv)	CD3+CD4+Treg-CD45RA+CCR7-
%Tconv Tscm (Tconv)	CD3+CD4+Treg-CD45RA+CCR7+CD95+
%Tconv Th1 (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5-CXCR3+CCR4-CCR10-CCR6-
%Tconv Th1Th17 (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5-CXCR3+CCR4-CCR10-CCR6+
%Tconv Th1Th2 (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5-CXCR3+CCR4+CCR10-CCR6-
%Tconv Th1Th17Th2 (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5-CXCR3+CCR4+CCR10-CCR6+
%TconvTh2 (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5-CXCR3-CCR4+CCR10-CCR6-
%TconvTh17 (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5-CXCR3-CCR4+CCR10-CCR6+
%TconvTh22 (mTconv)	CD3+CD4+Treg-Tconv Tn- Tconv Tscm-CXCR5-CXCR3-CCR4+CCR10+CCR6+
%Tconv Tfh (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5+
%Tconv PD-1+ ICOS+ Tfh (mTconv)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5+PD-1+ICOS+
%Treg Th1 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3+CCR4-CCR10-CCR6-
%Treg Th1Th17 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3+CCR4-CCR10-CCR6+
%Treg Th1Th2 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3+CCR4+CCR10-CCR6-
%Treg Th1Th17Th2 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3+CCR4+CCR10-CCR6+
%Treg Th2 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3-CCR4+CCR10-CCR6-
%Treg Th17 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3-CCR4+CCR10-CCR6+

Test Analyte	Details
%Treg Th22 (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5-CXCR3-CCR4+CCR10+CCR6+
%Treg Tfh (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5+
%Treg PD-1+ ICOS+ Tfh (mTreg)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5+PD-1+ICOS+
%Tconv PD-1+ ICOS+ Tfh (Tconv Tfh)	CD3+CD4+Treg-Tconv Tn-Tconv Tscm-CXCR5+PD-1+ICOS+ out of Tconv Tfh
%Treg PD-1+ ICOS+ Tfh (Treg Tfh)	CD3+CD4+CD25+CD127loTreg Tn-Treg Tscm-CXCR5+PD-1+ICOS+ out of Treg Tfh

10.8.2.3. Treg panel

Test Analyte	Details
%CD15s+ Tconv (Tconv)	CD3+CD4+CD25lo-medFOXP3-CD15s+
%CD69+ Tconv (Tconv)	CD3+CD4+CD25lo-medFOXP3-CD69+
%Helios+ Tconv (Tconv)	CD3+CD4+CD25lo-medFOXP3-HELIOS+
%Ki67+ Tconv (Tconv)	CD3+CD4+CD25lo-medFOXP3-KI67+
%CD15s+ mTconv (mTconv)	CD3+CD4+CD25lo-medFOXP3-CD45RA-CD15s+
%CD69+ mTconv (mTconv)	CD3+CD4+CD25lo-medFOXP3-CD45RA-CD69+
%Helios+ mTconv (mTconv)	CD3+CD4+CD25lo-medFOXP3-CD45RA-HELIOS+
%Ki67+ mTconv (mTconv)	CD3+CD4+CD25lo-medFOXP3-CD45RA-KI67+
%Treg (CD4)	CD3+CD4+CD25hiFOXP3+
%aTreg (Treg)	CD3+CD4+CD25hiFOXP3hiCD45RA-
%mTreg (Treg)	CD3+CD4+CD25hiFOXP3medCD54RA-
%rTreg (Treg)	CD3+CD4+CD25hiFOXP3medCD45RA+
%CD15s+ Treg (Treg)	CD3+CD4+CD25hiFOXP3+CD15s+
%CD69+ Treg (Treg)	CD3+CD4+CD25hiFOXP3+CD69+
%Helios+ Treg (Treg)	CD3+CD4+CD25hiFOXP3+HELIOS+
%Ki67+ Treg (Treg)	CD3+CD4+CD25hiFOXP3+KI67+
%CD69+ CD8 (CD8)	CD3+CD8+CD69+
%Ki67+ CD8 (CD8)	CD3+CD8+KI67+

10.8.2.4. Ratios of effector cells to regulatory cells

The following parameters are derived.

Test analyte	Details
Th1 Tconv:Treg	Th1 Tconv cell to Treg cell ratio Derivation: [%Tconv Th1 (mTconv)] / [%Treg Th1 (mTreg)]
Th1Th17 Tconv:Treg	Th1Th17 Tconv cell to Th1Th17reg cell ratio

Test analyte	Details
	Derivation: [%Tconv Th1Th17 (mTconv)] / [%Treg Th1Th17 (mTreg)]
Th1Th2 Tconv:Treg	Th1Th2 Tconv cell to Th1Th2reg cell ratio Derivation: [%Tconv Th1Th2 (mTconv)] / [%Treg Th1Th2 (mTreg)]
Th1Th17Th2 Tconv:Treg	Th1Th17Th2 Tconv cell to Th1Th17Th2reg cell ratio Derivation: [%Tconv Th1Th17Th2 (mTconv)] / [%Treg Th1 h1Th17Th2 (mTreg)]
Th2 Tconv:Treg ratio	Th2 Tconv cell to Th2reg cell ratio Derivation: [%TconvTh2 (mTconv)] / [%Treg Th2 (mTreg)]
Th17 Tconv:Treg ratio	Th17 Tconv cell to T17reg cell ratio Derivation: [%TconvTh17 (mTconv)] / [%Treg Th17 (mTreg)]
Th22 Tconv:Treg ratio	Th22 Tconv cell to Th22reg cell ratio Derivation: [%TconvTh22 (mTconv)] / [%Treg Th22 (mTreg)]
Tfh Tconv:Treg ratio	Tfh Tconv cell to Tfhreg cell ratio Derivation: [%Tconv Tfh (mTconv)] / [%Treg Thfh (mTreg)]

10.8.2.5. Suppressive activity of regulatory cells

Test Analyte	Details
Percentage suppression 0:1	Treg: Tconventional cell ratio 0:1
Percentage suppression 1:2	Treg: Tconventional cell ratio 1:2
Percentage suppression 1:4	Treg: Tconventional cell ratio 1:4

10.8.2.6. General Derivations

For the parameters in Section 10.8.2.1, Section 10.8.2.2 and Section 10.8.2.3, the percentages will be transformed into counts by multiplying by the denominator counts / 100. The denominator counts are given in brackets in the test analyte column.

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
BL	Baseline
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FNA	Fine needle aspirate
HV	Healthy volunteer
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
iLN	Inguinal lymph node
IMMS	International Modules Management System
GLMM	Generalized linear mixed model
GUI	Guidance
GSK	GlaxoSmithKline
NOT1D	New Onset Type 1 Diabetes Mellitus
PBMC	Peripheral blood mononuclear cell
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SOC	System Organ Class
TCR / BCR	T-cell Receptor / B-cell Receptor
TFL	Tables, Figures & Listings

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.nn	1.01 to 1.nn
Biomarker	2.01 to 2.nn	2.01 to 2.nn
Safety	3.01 to 3.nn	3.01 to 3.nn
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	SP_Fn	SP_Tn	SP_Ln
Biomarker	PD_Fn	PD_Tn	PD_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

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

10.10.3. Deliverable [Priority]

Delivery	Description
IA SAC	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.01	Enrolled	ES1	Summary of Subject Disposition		SAC
1.02	Screened	ES6	Summary of Screen Failures (Screened Subjects Population)		SAC
1.03	Enrolled	NS3	Summary of Subjects by Country and Centre		SAC
Population Analyzed					
1.04	Screened	SP1	Summary of Study Populations		SAC
Demographic and Baseline Characteristics					
1.05	Safety	DM1	Summary of Demographic Characteristics		SAC
1.06	Safety	DM5	Summary of Race and Racial Combinations		SAC
Current and Past Medical Conditions					
1.07	Safety	MH4	Summary of Past Medical Conditions		SAC
1.08	Safety	MH4	Summary of Current Medical Conditions		SAC
Concomitant Medications					
1.09	Safety	CM1	Summary of Concomitant Medications		SAC
Lymph Node Questionnaire					
1.10	Safety	SP_T1	Summary of Pre-Biopsy Lymph Node Questionnaire		SAC
1.11	Safety	SP_T1	Summary of Post-Biopsy Lymph Node Questionnaire		SAC

10.10.5. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Frequency and phenotype of leukocyte subsets by flow cytometry					
2.01	Safety	PD_T1	Summary of B_DC_Monocyte Panel by Method and Patient Group	Parameters listed in Section 10.8.2.1	IA SAC, SAC
2.02	Safety	PD_T2	Statistical Analyses of B_DC_Monocyte Panel by Method and Patient Group	Parameters listed in Section 10.8.2.1	IA SAC, SAC
2.03	Safety	PD_T1	Summary of T Cell Panel by Method and Patient Group	Parameters listed in Section 10.8.2.2	IA SAC, SAC
2.04	Safety	PD_T2	Statistical Analyses of T Cell Panel by Method and Patient Group	Parameters listed in Section 10.8.2.2	IA SAC, SAC
2.05	Safety	PD_T1	Summary of Treg Panel by Method and Patient Group	Parameters listed in Section 10.8.2.3	IA SAC, SAC
2.06	Safety	PD_T2	Statistical Analyses of Treg Panel by Method and Patient Group	Parameters listed in Section 10.8.2.3	IA SAC, SAC
2.07	Safety	PD_T1	Summary of ratios of effector cells to regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.4	IA SAC, SAC
2.08	Safety	PD_T2	Statistical Analyses of ratios of effector cells to regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.4	IA SAC, SAC
Suppressive activity of regulatory cells					
2.09	Safety	PD_T1	Summary of Suppressive activity of regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.5	IA SAC, SAC
2.10	Safety	PD_T2	Statistical Analyses of Suppressive activity of regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.5	IA SAC, SAC

10.10.6. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.01	Safety	AE1	Summary of Adverse Events Summary by SOC and PT		SAC
3.02	Safety	AE15	Summary of Common (>=5% incidence) Non-Serious Adverse Events by SOC and PT (No. of Subjects and occurrences)		SAC
3.03	Safety	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
Serious Adverse Events					
3.04	Safety	AE16	Summary of Serious Adverse Events by SOC and PT (No. of Subjects and occurrences)		SAC
3.05	Safety	AE1	Summary of Adverse Events Leading to Withdrawal from Study by SOC and PT		SAC
Vital Signs					
3.06	Safety	VS1	Summary of change from baseline in Vital Signs		SAC
3.07	Safety	VS7	Summary of Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		SAC

10.10.7. Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Frequency and phenotype of leukocyte subsets by flow cytometry					
2.01	Safety	PD_F1	Boxplots of B_DC_Monocyte Panel by Method and Patient Group	Parameters listed in Section 10.8.2.1	IA SAC, SAC
2.02	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of B_DC_Monocyte Panel	Parameters listed in Section 10.8.2.1	IA SAC, SAC
2.03	Safety	PD_F1	Boxplots of T Cell Panel by Method and Patient Group	Parameters listed in Section 10.8.2.2	IA SAC, SAC
2.04	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of T Cell Panel	Parameters listed in Section 10.8.2.2	IA SAC, SAC
2.05	Safety	PD_F1	Boxplots of Treg Panel by Method and Patient Group	Parameters listed in Section 10.8.2.3	IA SAC, SAC
2.06	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of Treg Panel	Parameters listed in Section 10.8.2.3	IA SAC, SAC
2.07	Safety	PD_F1	Boxplots of ratios of effector cells to regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.4	IA SAC, SAC
2.08	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of ratios of effector cells to regulatory cells	Parameters listed in Section 10.8.2.4	IA SAC, SAC
Suppressive activity of regulatory cells					
2.09	Safety	PD_F1	Boxplots of Suppressive activity of regulatory cells by Method and Patient Group	Parameters listed in Section 10.8.2.5	IA SAC, SAC
2.10	Safety	PD_F2	LS Mean Estimates and Differences with 95% CI of Suppressive activity of regulatory cells	Parameters listed in Section 10.8.2.5	IA SAC, SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screening Failure		SAC
2.	Enrolled	ES2	Listing of Reasons for Subject Withdrawal		SAC
3.	Screened	ES9	Listing of Subjects who were rescreened		SAC
Inclusion / Exclusion Criteria					
4.	Enrolled	IE3	Listing of Eligibility Criteria Not Met		SAC
Protocol Deviations					
5.	Enrolled	DV2	Listing of Important Protocol Deviations		SAC
Populations Analysed					
6.	Screened	SP3	Listing of Subjects excluded from any population		SAC
Demographic Characteristics					
7.	Enrolled	DM2	Listing of Demographic Characteristics		SAC
8.	Enrolled	DM9	Listing of Race and Racial Combinations		SAC
Current and Past Medical Conditions					
9.	Enrolled	MH2	Listing of Current and Past Medical Conditions		SAC
Prior and Concomitant Medications					
10.	Enrolled	CM3	Listing of Concomitant Medications		SAC
Adverse Events					
11.	Safety	AE8	Listing of All Adverse Events		SAC
12.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
13.	Safety	AE8	Listing of Serious Adverse Events (Fatal & Non-Fatal)		SAC
14.	Safety	AE8	Listing of Adverse Events Leading to Study Withdrawal		SAC
15.	Safety	AE14	Listing of Reasons for considering a serious AE		SAC
Laboratory					
16.	Safety	LB5	Listing of Laboratory Results: Hematology		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
17.	Safety	LB5	Listing of Laboratory Results: Clinical Chemistry		SAC
18.	Safety	UR2A	Listing of Laboratory Results: Urinalysis		SAC
Vital Signs					
19.	Safety	VS4	Listing of Vital Signs		SAC
20.	Safety	VS4	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC
Pregnancy					
21.	Safety	PREG1A	Listing of subjects who became pregnant during the study		SAC

10.10.8. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biopsy Details					
22.	Safety	PD_L3	Listing of Biopsy Sample Details		SAC
Lymph Node Questionnaire					
23.	Safety	SP_L1	Listing of Pre-Biopsy Lymph Node Questionnaire Data		SAC
24.	Safety	SP_L1	Listing of Post-Biopsy Lymph Node Questionnaire Data		SAC
Frequency and phenotype of leukocyte subsets by flow cytometry					
25.	Safety	PD_L1	Listing of B_DC_Monocyte Panel by Biomarker	Parameters listed in Section 10.8.2.1	IA SAC, SAC
26.	Safety	PD_L2	Listing of B_DC_Monocyte Panel by Group and Subject ID	Parameters listed in Section 10.8.2.1	IA SAC, SAC
27.	Safety	PD_L1	Listing of T Cell Panel by Biomarker	Parameters listed in Section 10.8.2.2	IA SAC, SAC
28.	Safety	PD_L2	Listing of T Cell Panel by Group and Subject ID	Parameters listed in Section 10.8.2.2	IA SAC, SAC
29.	Safety	PD_L1	Listing of Treg Panel by Biomarker	Parameters listed in Section 10.8.2.3	IA SAC, SAC
30.	Safety	PD_L2	Listing of Treg Panel by Group and Subject ID	Parameters listed in Section 10.8.2.3	IA SAC, SAC
31.	Safety	PD_L1	Listing of ratios of effector cells to regulatory cells by Biomarker	Parameters listed in Section 10.8.2.4	IA SAC, SAC
32.	Safety	PD_L2	Summary of ratios of effector cells to regulatory cells by Group and Subject ID	Parameters listed in Section 10.8.2.4	IA SAC, SAC
Suppressive activity of regulatory cells					
33.	Safety	PD_L1	Listing of Suppressive activity of regulatory cells by Biomarker	Parameters listed in Section 10.8.2.5	IA SAC, SAC
34.	Safety	PD_L2	Listing of Suppressive activity of regulatory cells by Group and Subject ID	Parameters listed in Section 10.8.2.5	IA SAC, SAC

10.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.