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

Title	:	Reporting and Analysis Plan for Study OTX116505: A Single Blind, Randomised, Placebo Controlled, Repeat Dose, Dose Escalating Study Investigating Safety, Tolerability Pharmacokinetics, Pharmacodynamics and the Beta Cell Preserving Effect of Otelixizumab in New-Onset, Autoimmune Type 1 Diabetes Mellitus Patients.
Compound Number	:	GSK2136525
Effective Date	:	20/NOV/2018

Description :

The purpose of this reporting and analysis plan (RAP) is to describe:

- The planned final analyses and output to be included in the Clinical Study Report for Protocol 2011N129686_09
- Describe the safety, tolerability, pharmacodynamic, pharmacokinetic and efficacy analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC) end of study deliverable

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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:

Revision Chronology:		
2011N129686_00	2013-SEP-05	Original
2011N129686_01	2014-FEB-27	Amendment No. 1
Addition of unblinded Pharmacy Monitor to table summarising blinding status of personnel; endpoint in table updated to include insulin measurement for 7 days before all outpatient visits; endpoint of glucose added when performing MMTT and clamp procedures; clarification of time period for collecting information in the screening period; removal of TCR complexes and clarification of CD3 requirements throughout protocol; change of volume required to purge the IV infusion line and total volume filled into syringe, and removal of "micopore" from description; the following changes to the Time and Events Tables: clarification that insulin should be recorded for 7 days before all outpatient visits; addition of Day 6 to footnote 18; clarification that glucose will be collected in addition to C-peptide during the hyperglycaemic clamp procedure (Section 6.2.2); addition of ECGs at 6 hours post start of infusion (Section 6.2.3) clarification of which ECGs will be triplicate or single measures; addition of TCR deep sequencing at 24 months to Biomarker Assay Table; clarification that MMTT will be at least 7 days prior to the first dose of study drug; clarification that c-peptide and glucose samples will be shipped within 3 weeks of collection; clarification that the hyperglycaemic range of 180-240mg/dL during 140 minutes for consistency with blood sampling time points.		
2011N129686_02	2014-APR-02	Amendment No. 2
Hyperglycaemic events is included in the follow up endpoints and the Time and Events table to be consistent with the applicable secondary objective; rephrased "Immuno-Assay for syphilis test" in order to allow for different types of tests; increased the overage volume required to remain in the syringe for infusion; clarified the start of AE recording.		
2011N129686_03	2014-JUN-18	Amendment No. 3
The third medical monitor has changed, therefore contact information for the replacement is included. The eligibility inclusion criterion was changed from two to one positive autoantibody associated with TIDM.		
2011N129686_04	2014-JUL-28	Republishing-Amendment No. 3
Clarified that within each cohort administration of study treatment for the first three patients will be staggered by at least three days across each centre.		
2011N129686_05	2015-FEB-11	Amendment No. 4
To increase flexibility for patients, dosing on Day 4, 5 & 6 may be performed on an out-patient basis if the Investigator is satisfied with the clinical status of the patient; clarification that if the infusion needs to be reduced or temporarily stopped the Investigator should first consult with the Medical Monitor who will consult the Sponsor, unless there is an immediate safety hazard, in this case the Investigator can inform the		

Medical Monitor afterwards; clarified that insulin use is to be recorded prior to each visit and phone call; clarification that the decision to replace a patient is to be based on the reason for withdrawal; inclusion criteria # 3 amended; screen failure data are to be collected; assessments following patient withdrawal clarified; clarified that infusion kits are supplied to sites; assessment of EBV reactivation now conducted at 6 weeks after the first active dose (reduced from 12 weeks); blinding status amended to clarify that only the patient is blinded and not site staff; requirement for pharmacy staff to document that investigational product shipping conditions were 2-8°C included; anti-emetic added as a permitted concomitant medication, window of ± 1 day added to Day 14 and 21 visits and Week 4 telephone call; Section 6.2.2 amended to include a phone call at Week 4 to discuss AEs with patient and addition of assessments at Week 6; endpoints amended to reflect the change to visits at Week 4 and Week 6; Section 6.2.3 amended to include ECG at 3 hours and to clarify that assessments may stop at 3 hours post dose; clarification of cytokine release syndrome adverse events grading system and stopping criteria in Section 7.1.5; clarification on requirements for bilirubin samples included; CRO responsibilities clarified and supply of Ensure powder by CRO/GSK included.		
2011N129686_06	2015-AUG-18	Amendment No. 5
The assay for screening EBV IgG and IgM assessment was clarified in exclusion criterion number 18 and in Table 2 in the Risk Management section; exclusion criterion 18 was split into two exclusion criteria (18 and 19) to clarify EBV IgM, IgG and Viral load requirements for the interpretation of the results: a footnote was added to Table 6 (Stopping Criteria for CRS-Adverse Events) to provide further clarification regarding when individual stopping criteria are met; the dose preparation section was updated to clarify that an additional maximum of 30 minutes is allowed for dose preparation tasks and that if 6 hours is exceeded, the syringe and infusion materials must be replaced; EBV serology samples to assess IgG and IgM included for Day -1 in the Time and Events Table (Table 6.2.2 Dosing and Follow-Up).		
2011N129686_07	2016-SEP-12	Amendment No. 6
Clarifications were made to the exploratory biomarker objectives and endpoints. Significant changes were: the addition of Th17 cells to the objective to assess the effect of otelixizumab on circulating lymphocytes; the addition of viral antigens to the endpoints to assess the effect of otelixizumab on the frequency of cytokine-producing antigen specific T cells; the addition of transcriptomic gene expression changes to the objective to assess the effect of otelixizumab on the clonal repertoire of circulating T cell populations; and clarification that the suppression activity of circulating T lymphocytes may be further evaluated by adapting assay conditions, possibly through adding and/or blocking of stimuli. The Time and Events table was updated to show requirement for telephone calls at Month 36, 48 and 60. Month 24 exploratory biomarkers are now being routinely collected and are not subject to the results of Month 12 biomarker analysis. In addition, it was clarified that Month 24 exploratory biomarker samples will be collected and only analysed after review of safety endpoints from Month 12 and not efficacy endpoints as previously stated. Minor clarifications related to the Month 12 Interim Analyses were included.		

The name Quest was amended to Q^2 Solutions and Study Procedures Manual was changed to Study Reference Manual.		
2011N129686_08	2017-SEP-11	Amendment No. 7
All details of how the currently used Ensure powder (Abbott) is prepared has been removed from the Mixed Meal Tolerance Test (Appendix 5). This has been amended because the manufacturer (Abbott) has discontinued the currently used powder and the new product has a slightly different formulation. The details for each of the products will now be detailed in the Study Reference Manual.		
2011N129686_09	YYYY-MMM-DD	Amendment No. 8
Data which emerged from an interim analysis carried out in this study showed a prompt regain of immune competence observed in treated subjects and consequent rapid resolution of EBV reactivation, both clinically and virologically. The long term EBV related PTLD risk, as observed in solid organ transplant on a chronic immune suppression therapy, is negligible. Therefore, all references to month 48 and 60 have been removed as no patient currently enrolled in the study has reached month 48 of follow up. For the patients who have yet to complete their 24 month visit, this visit will be treated as a final visit and for those who have gone past month 24, they will be followed up with a final communication or visit (final follow up) upon approval of this protocol amendment. Data from the literature identified a causal relationship between the degree of immunosuppression and an increased incidence of EBV related Post Transplant Lymphoprolerative Disorders (PTLD) and for this reason a long-term follow-up was implemented at the start of the study.		

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Interim Reporting and Analysis plan OTX116505 [08-Dec-2014]	
Reporting and analysis Plan OTX116505 Amend 1 [30-Sep-2015]	
• 2.2, 2.3	• Study objectives, endpoints and design updated to reflect protocol amendment 5.
• 4	• Added in a 'Fully treated' population for use in key efficacy endpoints.
• 6.2	• Inclusion of a listing of concomitant medication during the dose escalations.
• 7.1.2.1	• Inclusion of additional safety outputs during the dose escalations.
• 8.2.2.1	• Additional sentence explaining the use of 'Fully Treated' population for Key efficacy outputs.
• 11.2.3	• Updated time and events table based on protocol amendment 5.
• 11.2.4	• Updated time and events table based on protocol amendment 5.

RAP Section	Amendment Details
• 11.3	• Baseline information added for antibody endpoints. RTF files will be produced for displays.
• 11.4.2	• Explanation of the derivation of a positive/negative value for the EBV IGm/IGg endpoint added
• 11.5.1	• Sentence added explaining that data after a subject withdraws will be listed and flagged
• 11.5.3	• Explanation regarding handling of partial dates added.
• 11.6	• Update to PCI ranges
• 11.9	• Inclusion of additional outputs as explained in sections 6.2, 7.1.2.1 and 8.2.2.1
Reporting and analysis Plan OTX116505 Amend 2 [01-Nov-2016]	
• 2.1	• Updated to reflect changes to protocol amendment dated 12SEP2016
• 2.2	• Exploratory Endpoints updated to reflect changes to protocol amendment dated 12SEP2016
• 3.1	• Updated Interim analysis specifications to reflect changes to protocol amendment dated 12SEP2016 • Clarification to process for delivering tables
• 4	• Biomarker endpoints added to ITT • HLA-A2 Positive Population added
• 9	• New section to describe Exploratory Biomarker analysis
• Appendix 8	• New section to describe Exploratory Biomarker analysis
• 11.4.3	• Clarification to Laboratory parameters
• Appendix 10 and 11	• Addition of Biomarker TLFs • Corrections and clarifications based on PXL review.

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 dated on the 26 Oct 2017 for the study GSK2136525/OTX116505 (GSK Document No. : 2011N129686_09).

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

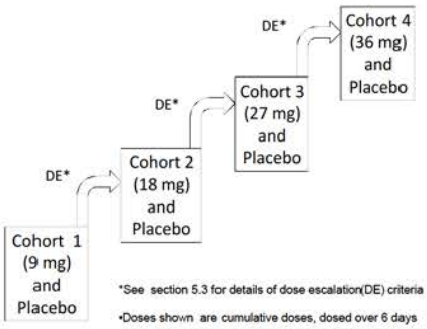
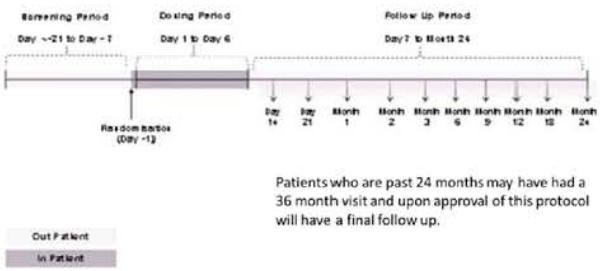
Primary	
Primary Objectives (Safety)	**Primary Endpoints (Safety)**
• To assess the effect of a single course of otelixizumab treatment on the acute and long term safety and tolerability of otelixizumab in NOT1DM patients.	• Incidence of adverse events (AEs) particularly those related to Cytokine release syndrome (CRS). • Epstein-Barr virus (EBV) reactivation over Day 21 to Month 24. • Changes in laboratory values, electrocardiograms (ECGs) and vital signs over Day 14 to Month 24.

Secondary	
Secondary Objectives (Pharmacokinetic)	**Secondary Endpoints (Pharmacokinetic)**
• To assess the pharmacokinetics of repeat dose administration of otelixizumab over 14 days in NOT1DM patients.	• Free serum otelixizumab concentrations over Days 1-14 and summary PK parameters.
Secondary Objectives (Efficacy)	**Secondary Endpoints (Efficacy)**
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of pancreatic β-cell function over 24 months in NOT1DM patients.	• Change from baseline in C-peptide and glucose AUC (0-120) after a Mixed Meal Tolerance Test at Month 3, 6, 12, 18 and 24.
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of C-peptide response and insulin sensitivity of β -cell function determined after a hyperglycemic clamp over 24 months in NOT1DM patients.	• Change from baseline in C-Peptide and glucose AUC hyperglycemic phase [H60 to H140 minutes] and insulin sensitivity (IS) index after a hyperglycemic clamp at Months 6 and 24.
• To assess the effect of a single course of otelixizumab treatment on exogenous insulin use for otelixizumab over 24 months in NOT1DM patients.	• Change from baseline in mean daily insulin use over 7 consecutive days during the week preceding all visits and phone calls.
• To assess the effect of a single course of otelixizumab treatment on glycaemic control over 24 months in NOT1DM patients.	• Change from baseline in HbA1c level. • Body weight Day -1, Months 12-24. • Hypoglycemic & hyperglycemic events over Months 1-24.
Secondary Objectives (Pharmacodynamic)	**Secondary Endpoints (Pharmacodynamic)**
• To assess the effect of a single course of otelixizumab treatment on the time course and magnitude of CD4+ and CD8+ cells and CD3 binding and saturation on all these cells during repeat dose administration of otelixizumab	• Relative change from baseline (%) in CD4+ and CD8+ cells, free CD3 and bound otelixizumab on CD4+ and CD8+ cells on Days 1 through 14.

over 14 days in NOT1DM patients.	
• To assess the effect of a single course of otelixizumab treatment on the immunogenicity of otelixizumab in NOT1DM patients.	• Change from baseline in anti-drug antibody levels at Months 3 and 6.
Exploratory Objectives *	**Exploratory Endpoints ***
• To assess the effect of a single course of otelixizumab treatment on circulating lymphocyte populations over 24 months in NOT1DM patients.	• Change from baseline in absolute lymphocyte counts and ratios in some or all, but not limited to subsets (CD3+ CD4+, CD3+ CD8+, and CD19+ cells) and phenotype (e.g. effector, memory, regulatory T cells, e.g. CD45RA, CCR7+) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on circulating lymphocutes such as regulatory T cell numbers (as quantified by CD3 and demethylated FoxP3 expression) and Th17 cells over 24 months in NOT1DM patients.	• Change from baseline in cell-type specific methylation marker expression in some or all, but not limited to CD3, FoxP3 and Th17 in whole blood over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on absolute numbers and ratios of circulating antigen specific CD8+ T cells over 24 months in HLA-A2^{+} NOT1DM patients.	• Change from baseline in absolute numbers and ratios of HLA-A2-restricted CD8 T lymphocytes reactive to specific auto-antigens (by multimer) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on frequency of cytokine-producing antigen specific T cells over 24 months in NOT1DM patients.	• Change from baseline in frequency of cytokine producing cells following in vitro stimulation with auto-antigens and viral antigens (by ELISPOT) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on serum auto-antibodies titers and serum analytes associated with treatment or autoimmune pathology over 24 months in NOT1DM patients.	• Change from baseline in auto-antibody titres (using a panel of common auto-antibodies associated with T1DM antigens and possibly other auto-antigens) and serum analytes (such as cytokines/ chemokines) during the first 14 days of treatment and over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on clonal repertoire of circulating T cell populations and/or transcriptomic gene expression changes over 24 months in NOT1DM patients.	• Change from baseline in T cell clonal repertoire by TCR deep sequencing over Day 6 to Month 24. • Change from baseline in transcriptomic gene expression profile(s) by micro-array and/or alternative equivalent technologies including RNA sequencing at selected timepoint(s) post dosing.
• To assess the effect of a single course of otelixizumab treatment on β-cell death over 24 months in NOT1DM patients.	• Change from baseline in serum by measuring relative levels of unmethylated *INS* DNA and/or other biomarkers for β-cell death in serum over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on suppression activity of circulating T lymphocytes over 24 months in NOT1DM patients.	• Change from baseline in relative levels of T lymphocyte suppression using micro suppression assay over Week 6 to Month 24. Suppression activity may be further evaluated by adapting assay conditions possibly through adding and/or blocking of stimuli.

Follow up Objectives	Follow up Endpoints
• To assess long term safety follow-up with otelixizumab treatment.	• Significant adverse events. • Severe (as per ADA classification, Protocol Appendix 7) hypoglycemic events which occurred following Month 24 visit (if available) until final follow-up • Severe hyperglycemic events which occurred following Month 24 visit (if available) until final follow-up • Mean daily insulin use over 7 consecutive days preceding the call. • HbA1c results around time of the phone call.
*Samples will be collected and only analysed after review of safety endpoints	

2.3. Study Design

Overview of Study Design
 
Note: the study design shown is the original study design. Stopping criteria for escalation was met in Cohort 3. In addition, the duration of the study has been shortened to 24 months.

Overview of Key Study Design Features	
Design Features	• Multi-centre, single-blind, randomised, placebo-controlled 6 day repeat dose study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy & immunological profile of intravenously administered otelixizumab in New Onset Type 1 Diabetes Mellitus (NOT1DM) patients.
Dosing	• Patients dosed within ~ 28 days of diagnosis (not more than 32 days). • Insulin usage documented for ~ 7 days prior to screening & Day -1 (baseline). • There will be a 7-21 day period from screening to admission to the clinic on Day -2 for the first overnight stay of the in-patient period. • Patients randomised on Day -1 followed by a hyperglycaemic clamp test. • Dosing will start on Day 1 & patients will remain in unit for IV dosing. • Patients will be given the following flexible options for dosing on Days 4, 5 and 6: Option 1: Receive study treatment on an out-patient basis on any of Days 4, 5 or 6, if the Investigator is satisfied with the clinical condition of the patient. Option 2: Patients will remain in the unit if there are any concerns about their clinical status, or if the patient prefers to remain in the unit for logistical reasons. • **NOTE:** Within each cohort administration of study treatment will be staggered by at least three days for the first three patients across each centre.
Treatment Assignment	• Approximately 32 patients will be dosed in a dose escalation design exploring 4 dose cohorts (4 dose levels (9, 18, 27,36) and placebo). • At each dose cohort 8 patients will be randomised to otelixizumab and 2 patients to placebo.
Interim Analysis	• The planned protocol defined unblinded interim analyses were:

	○ Ongoing data reviews throughout the trial progression. ○ Data reviews to assess whether to dose escalate to the next cohort. ○ 12 months formal interim analysis.

2.4. Statistical Hypotheses

The protocol defined hypotheses were defined as:

- As the primary objective is to assess the safety, tolerability and maximum tolerated dose of Otelixizumab in participants with NOT1DM patients, there are no formal hypotheses being tested in the study; instead an estimation and inference approach will be adopted to evaluate the objectives.
- If data permits, a model-based approach will be used to characterise and assess any evidence of dose response relationships with endpoints of interest.

3. PLANNED ANALYSES

3.1. Interim Analyses

The interim analyses are described in the interim RAP, Amendment 2, dated 01-Nov-2016 and include the following.

Interim Analysis	Details (Protocol Defined)
During The Study	• There will be ongoing data reviews conducted by the study team of the unblinded safety and efficacy data, and any available pharmacokinetic and pharmacodynamic data throughout the trial progression.
Dose Escalation	• Further unblinded data reviews of safety data will be performed to support whether to dose escalate to the next cohort. If deemed appropriate, the review may also include supportive pharmacokinetic, biomarker or pharmacodynamic data if available. Details are provided below: ○ Data will be reviewed after 10 patients have been dosed in cohort 1 (8 patients on otelixizumab 9 mg and 2 patients on placebo) and have completed approximately 6 wks of the study and required data is available. ○ If required, data reviews prior to 6 wks may also be conducted to facilitate dose escalation to the next cohort. ○ It is not expected that this review will occur on fully cleaned data. ○ Further data reviews based on criteria provided for cohort 1, will be performed for subsequent cohorts, including an overall review of accumulated data across the cohorts. ○ Core members of the dose escalation review team will include the principal investigator (Chief), medical monitor, GCSP, clinical pharmacologist, study leader & statistician. Other GSK and CRO study team members may be

Interim Analysis	Details (Protocol Defined)
	included as required.
12 Months	• A formal unblinded interim analysis is also planned to occur. • The first interim will occur when all patients in cohorts 1 and 2 have completed 12 months study duration, but may also include any available data from subsequent cohorts 3 and 4 as appropriate. • The second interim analysis will occur when all patients from the last fully enrolled cohort (i.e. not stopped due to safety / tolerability) have completed 12 months study duration. The purpose of this interim analysis is to provide the project team and GSK stakeholders with key data to inform internal decision making, in order to plan future studies within the clinical development for the asset. • There are no planned implications for the conduct of the study. • Appropriate data summaries will be at the treatment group level for key endpoints of interest and the circulation of results will be restricted to selected members of the project team and key GSK stakeholders. Results or discussions will not be circulated to blinded staff involved in the conduct of the study at the sites. • Note: Because of the anticipated time frame to process and analyse the biomarker data they will not be included in the SAC deliverables. Therefore all other data may be frozen and the study unblinded before they are available. Once the data become available they will be added to the other frozen datasets and analysed as described

3.2. Final Analyses

The following final planned analyses will be performed and details will be provided in this RAP.

Analysis	Details
Final Primary Analyses (24 Months)	The final analysis will occur when the last planned cohort (i.e. based on the dose escalation criteria) have completed 24 months study duration or have had a final follow-up for subjects who, at the time of the implementation of Amendment 08 of the protocol, will have already reached months 24.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated

Population	Definition / Criteria	Endpoint(s) Evaluated
Screened Population	• All participants who were screened for eligibility	• Study Population • Screening Failures
Randomized Population	• All participants who were randomly assigned to a study treatment • In summary tables, the treatment the subject was randomized to will be used	• Study Population
Enrolled Population	• All participants who passed screening, signed informed consent and entered the study. This includes: o Run-in failures o Randomised participants • Screening failures are not included	• Assignment to Analysis Populations
Safety Population	• Comprise of participants who receive at least one dose of study treatment. • This population will be based on the treatment which the participant actually received.	• Study Population • Safety • Pharmacodynamic
Intent-To-Treat (Treated)	• Comprise of all randomised participants who receive at least one dose of study treatment. • This population will be based on the treatment to which the participant was randomised.	• Efficacy • Biomarker
Per-Protocol Population (Treated)	• Comprise of all randomized participants who receive at least one dose of study treatment and who comply with the protocol. • Protocol deviations that would exclude participants from the PP population are defined in the Protocol Deviation Management Plan (PDMP) Version 2.5, dated 25-Jul-2018. If the PDMP is updated after signature of the SAP and before database lock, then the newest version will be used instead.	• As required based on data and exclusion of participants.
Fully treated	• Comprise of all randomized participants who receive the full 6 days of treatment based on actual exposure data.	• Population may also be used for the key efficacy endpoints • Population may be used for PK and biomarker analyses
Multimer Analyses Population	• Comprises of all Intent-to-treat (Treated) who have available multimer data	• Biomarker (Multimer Analysis)
NOTES :		

Population	Definition / Criteria	Endpoint(s) Evaluated
• Please refer to Appendix 10: List of Data Displays, which details the population for each display generated. • As there are no planned pharmacokinetic analyses, this population will be defined for the next reporting effort.		

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 summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study according to the Protocol Deviation Management Plan. Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorized 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 deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion form.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Study Treatment Descriptions			
Code	**Description**	**Description**	**Order [2]**
A	Otelixizumab 9 mg	OTX 9 mg	2
B	Otelixizumab 18 mg	OTX 18 mg	3
C	Otelixizumab 27 mg	OTX 27 mg	4
P [1]	Placebo	Placebo	1

NOTES :

[1] Placebo will be pooled across cohorts for analysis and reporting.

[2] Order in which treatments are to be presented in Tables, Figures and Listings.

Due to protocol amendments, there have been some changes in the scheduling of certain assessments. Listings will show the visit according to the schedule according to the protocol version used, while for summary tables the following rules shall apply:

- In general, if for an endpoint some participants have a Week 4 assessment, while other subjects have a Month 1 assessment (e.g. mean insulin usage), it will be summarized under Week 4.
- For vital signs, haematology, clinical chemistry, biomarkers and Epstein-Barr virus serology, the time points Month 1 and Week 6 shall be combined and displayed as "Month 1/Week 6" with an explanatory footnote.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. OTX 9 mg vs Placebo
2. OTX 18 mg vs Placebo
3. OTX 27 mg vs Placebo

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose 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 first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

As triplicates are taken for the baseline ECG data, the average will be used as baseline. If one or two of the triplicate measurements are missing, the remainding measurement(s) will be used to calculate the average. For categorical variables for triplicate ECG assessments the worst case will be used. In terms of worseness this is defined as abnormal, clinically significant > abnormal, clinically insignificant > normal > unable to evaluate.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Table 1 provides an overview of appendices within the final 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.
- There are known discrepancies between the terminology subject vs participant used across Protocols and RAP. All displays will use the term 'Subjects'.
- In the following the use of the word "log" is to be understood to refer to the natural logarithm (base e) unless another base is specifically stated

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Schedule of Activities
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Study Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Biomarker Analyses
11.9	Appendix 9: Abbreviations & Trademarks
11.10	Appendix 10: List of Data Displays
11.11	Appendix 11: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

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

Full details of data displays being presented in Appendix 10: List of Data Displays.

6.2. Exposure

Cumulative dose, days on study drug and daily infusion duration in hours for each dosing day will be summarised.

6.3. Concomitant Medication and Insulin Usage

All concomitant medication will be summarised and listed as per GSK Core Data Standards. To aid review of concomitant medications, the data collected for the daily insulin use will be listed separately.

7. SAFETY ANALYSES

The safety analyses will be based on the "Safety" population, unless otherwise specified. Due to the long duration of the study safety summaries will be presented for the following time spans: Overall, Dosing Period (defined as day of first dose up to and including day of last received dose of study drug), Post dose up to Week 6, Post-Week 6. A definition is found in Section 11.3.

7.1. 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.

No separate outputs will generated for Common AEs (more than 5% incidence in any treatment group) as the sample size means all occurrences would be considered common. A footnote will be added to the all AE overview, that all categories count as common.

In case of liver monitoring/stopping events, the outputs required by GSK guidelines will be produced. Those output are not listed in Section 11.10.

7.2. Adverse Events Related to CRS and EBV Reactivation

Adverse Events associated with Cytokine Release Syndrome (CRS) induced symptoms and events associated with EBV reactivation will be summarised as per section 7.1 as well as summarised in separate outputs.

See Section 11.5.3 for details on selection of AEs related to CRS and EBV reactivation. The details of the planned displays are provided in Section 11.10: List of Data Displays.

7.3. EBV Serology and Viral Load

EBV Serology will be listed and summarised using frequency of positive/negative values at each visit as described in Section 11.5.3.

EBV Viral Load will be listed and summarised using summary statistics using a log-10 transformation. Frequency of number of copies per 10^6PBM Cells will presented as described in Section 11.5.3.

7.4. Cardiovascular Events

Event Specific data will be listed if there are any occurences of cardiovascular events. If there are no events these listings will not be produced.

7.5. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Section 11.10.

7.6. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Section 11.10: List of Data Displays.

8. PHARMACOKINETIC ANALYSES

8.1.1. Drug Concentration Measures

Blood sampling time will be related to the start of dosing. Linear and semi-logarithmic individual serum concentration-time profiles and mean (±SD) and median profiles will be plotted by treatment.

Serum concentrations of otelixizumab will be listed and summarised by treatment group and nominal time.

Refer to Section 11.4 for the reporting process and standards.

8.2. Derived Serum Pharmacokinetic Parameters

- Free serum otelixizumab pharmacokinetic parameters will be calculated using SAS. Calculations will be based on the actual sampling times recorded during the study.

- From the serum concentration-time data, the pharmacokinetic parameters in Table 2 will be determined for free serum otelixizumab, as data permit, for each treatment and for each participant.

- **Table 2 Derived Pharmacokinetic Parameters**

Parameter	Parameter Description
Cmax	Maximum observed serum concentration
tmax	Time to Cmax
AUC(0-τ)	Area under the serum concentration-time curve from time zero over the dose interval

NOTES: Additional parameters may be included as required.
AUC(0-τ) will be calculated using the trapezoidal rule (see section 11.5.4) and will use all timepoints up to and including Day 6, 1 hour post dose.

9. EFFICACY ANALYSES

9.1. Overview of Planned Efficacy Analyses

Following review of the data, additional analyses may be conducted to further support the evaluation and interpretation of the data. Details of data displays being presented in Section 11.10: List of Data Displays.

9.1.1. Endpoints / Variables

The following endpoints will be analysed:

- Change from Baseline in Weighted Mean AUC (0-120) C-Peptide & Glucose from MMTT
- Change from Baseline in Weighted Mean AUC [(60-140)] C-Peptide & Glucose from Hyperglycemic Clamp Test
- Change from Baseline in Insulin Sensitivity Index from Hyperglycemic Clamp Test
- Change from Baseline in Mean Daily Insulin Use
- Change from Baseline in %HbA1c
- Change from Baseline in Body Weight
- Hypoglycemic and hyperglycemic events over Months 1-24.
- Number (percent) of participants meeting responder status on C-peptide from MMTT
- Number (percent) of participants achieving partial remission status
- Number (percent) of participants achieving HbA1c Responder Status

For detailed derivations of the efficacy endpoints please see Section 11.5.4.

9.1.2. Summary Measure

For continuous measures the treatment comparison will be the difference between treatment means at each visit. If log transformation is required the treatment comparison will be the ratio of treatment means at each visit.
For responder endpoints the treatment comparison will be the difference in % of responders in each treatment group.

9.1.3. Population of Interest

The efficacy analyses will be based on the Intent-To-Treat (Treated) population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

No imputation of missing data will be performed.

9.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Section 11.10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Responder endpoints will be summarised only.

9.1.5.1. Statistical Methodology Specification - MMRM

Endpoints

- Change from Baseline in Weighted Mean AUC (0-120) C-Peptide & Glucose from MMTT
- Change from Baseline in Weighted Mean AUC [(60-140)] C-Peptide & Glucose from Hyperglycemic Clamp Test
- Change from Baseline in Insulin Sensitivity Index from Hyperglycemic Clamp Test
- Change from Baseline in Mean Daily Insulin Use
- Change from Baseline in %HbA1c
- Change from Baseline in Body Weight

Model Specification

- Endpoints will be statistically analysed using a mixed model repeated measures (MMRM) model.

Terms fitted in the MMRM model will include:

- Fixed Categorical: Treatment, Visit, Treatment * Visit Interaction
- Fixed Continuous Covariates: Baseline #
- Repeated: Visit

Other covariates may be added using the following procedure:

For each covariate the MMRM model for the MMTT C-peptide analysis using the ITT population will be expanded and fitted two times:

1. Only the covariate will be added as an additional fixed factor
2. Both the covariate and the interaction of the covariate with treatment will be added as fixed factors

If the covariate is significant at a 10% alpha level using Type III p-values in the first model, then the covariate may be added to all MMRM models of efficacy endpoints or specific analyses may be repeated with the covariate added. When the interaction between the covariate and treatment is significant at a 10% alpha level in the second model, then both the covariate and the interaction of the covariate with treatment may be added.

The following covariates will be considered: BMI, Weight, Number of positive Auto Antibodies (categorical, 1 or > 1; see Section 11.5.3 for derivation).

The p-values for the tests described above will be presented in the statistical listing for the MMTT C-peptide analysis.

Model Checking Assumptions

- Model assumptions will be applied, but appropriate adjustments may be 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 REPEATED line.
  - In the event that this model fails to converge, alternative correlation structures may be considered such as Spatial Power Model, CSH or CS. The correlation structure chosen should make sense and not just chosen because model converges (e.g. AR(1) would not be appropriate as the visit structure is not even).
  - 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.
- All model checking will be presented in a statistical listing along with the raw SAS output from the analyses.

Presentation of Results

- Adjusted means (Value and Change from Baseline) and corresponding standard error of means (SEs) and 95% confidence intervals will be presented for each treatment by time, together with estimated treatment differences and the corresponding 95% confidence intervals.
- Plots of LS means =/- SE from the model will be generated for each treatment by time. Additionally, plots of differences and 95% confidence intervals for the comparison of interest will be generated.

Sensitivity and Supportive Analyses

- A supportive analysis using the 'Fully Treated' population will be performed for the following endpoints:
  - Change from Baseline in Weighted Mean AUC (0-120) C-Peptide & Glucose from MMTT
  - Change from Baseline in Weighted Mean AUC (60-140) C-Peptide & Glucose from Hyperglycemic Clamp Test

9.2. Overview of Planned Pharmacodynamic Analyses

9.2.1. Endpoints / Variables

The following endpoints will be analysed:

- Relative change from baseline (%) in CD4+ and CD8+ cells, free CD3 and bound otelixizumab on CD4+ and CD8+ cells on Days 1 through 14.

9.2.2. Summary Measure

The target engagement variables (see Section 11.5.5 for a detailed listing and derivations) will be summarized. The treatment comparison will be the difference between treatment means at each visit.

9.2.3. Population of Interest

The pharmacodynamic analyses will be based on the Fully Treated Population unless otherwise specified. Listings will be created using the Safety Population.

9.2.4. Strategy for Intercurrent (Post-Randomization) Events

No imputation of missing data will be performed.

9.2.5. Statistical Analyses / Methods

Analysis will be restricted to summary statistics. Details of the planned displays are provided in Section 11.10: List of Data Displays and will be based on GSK data standards and statistical principles.

9.3. Pharmacokinetic / Pharmacodynamic Analyses

No PK/PD Analyses are considered to be in the scope of this RAP.

9.4. Overview of Planned Exploratory Analyses

9.4.1. Endpoints / Variables

The following endpoints will be analysed as available:

- Frequency and phenotype of lymphocyte subsets by flow cytometry
- Frequency and phenotype of lymphocyte subsets by flow cytometry by C-peptide Responder Status
- Frequency and phenotype of HLA-A2-resticted T1D- and EBV-specific CD8+ T cells by multimer analysis
- Quantification of serum cytokines and soluble cytokine receptors
- Percentage Productive clonality by TCR deep sequencing

Due to data quality the remaining biomarker data will be listed only:

Details of data displays being presented in Section 11.10.

Further details of the endpoints to be considered is presented in Section 11.8.

9.4.2. Summary Measure

For continuous measures the treatment comparison will be the difference between treatment means at each visit. If log transformation is required the treatment comparison will be the ratio of treatment means at each visit.

9.4.3. Population of Interest

Figures will be based on the Fully Treated Population. For the other outputs the ITT Population will be used, with the exception of the multimer analysis, which will be performed using the Multimer Analyses Population.

9.4.4. Strategy for Intercurrent (Post-Randomization) Events

No imputation of missing data will be performed.

9.4.5. Statistical Analyses / Methods

Analysis will be restricted to summary statistics. Details of the planned displays are provided in Section 11.10: List of Data Displays and will be based on GSK data standards and statistical principles.

10. REFERENCES

1. GlaxoSmithKline Document Numbers 2011N129686_00 (Original – 05-Sept-13), 2011N129686_01 (Protocol Amendment – 27-Feb-14), 2011N129686_02 (Protocol Amendment – 02-APR-14), 2011N129686_03 (Protocol Amendment – 28-JUN-14), 2011N129686_04 (Republish Protocol Amendment – 28-JUL-14), 2011N129686_05 (Protocol Amendment – 11-FEB-15), 2011N129686_06 (Protocol Amendment – 18-AUG-15), 2011N129686_07 (Protocol Amendment – 12-SEP-16), 2011N129686_08 (Protocol Amendment – 11-SEP-17), 2011N129686_09 (Protocol Amendment – 26-OCT-17): A Single Blind, Randomised, Placebo Controlled, Repeat Dose, Dose Escalating Study Investigating Safety, tolerability Pharmacokinetics, Pharmacodynamics and the Beta-Cell Preserving Effect of Otelixizumab in New-Onset, Autoimmune Type 1 Diabetes Mellitus Patients.
2. GlaxoSmithKline Interim Reporting and Analysis Plan OTX116505 (Original – 08-Dec 2014), Interim Reporting and Analysis Plan OTX116505 Amendment 1 (30-Sep-2015), Interim Reporting and Analysis Plan OTX116505 Amendment 2 (01-Nov-2016).
3. Mortensen, H. B., et al. (2009). "New definition for the partial remission period in children and adolescents with type 1 diabetes." Diabetes Care 32(8): 1384-1390.
4. Long, S. A., et al. (2016). "Partial exhaustion of CD8 T cells and clinical response to teplizumab in new-onset type 1 diabetes." Sci Immunol 1(5).
5. DeFronzo, R. A. et al. (1979). "Glucose clamp technique: a method for quantifying insulin secretion and resistance." Am. J. Physiol. 237(3).

11. APPENDICES

11.1. Appendix 1: Schedule of Activities

11.1.1. Protocol Defined Time & Events

11.1.2. Screening

Medication history
Full physical examination (including height and weight)
Drug/alcohol history
Chest X-ray (to rule out TB)
Serology (EBV, HIV, Hep C, Hep B, Syphillis)
12-lead ECG in triplicate
Vital signs (including temperature, blood pressure and pulse rate (in triplicate) and respiration rate
Urine Pregnancy test (female only)
Haematology (must include total lymphocyte count)
Clinical Chemistry
T1DM Auto antibody (Anti-GAD, anti-IA2, antibody to islet cell antigen (ICA), anti-ZnT8)
EBV Viral Load (PCR)
AE assessment

The following must be performed at least 7 days prior to dosing
Mixed Meal Stimulated C-peptide (MMTT)

11.1.3. Dosing and Follow-Up

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36 month (if applicable) and/or final follow up
Patient admitted to unit[1]	X																			
In Patient		X	X	X	X	X[2]	X[2]	X[2]												
Prophylaxis then IV Dosing of study treatment			X	X	X	X	X	X												
Patient Discharged[2]								X												
Out Patient#						X	X	X	X	X		X	X	X	X	X	X	X	X	
Telephone call or out-patient visit to collect AEs, hypoglycemic and hyperglycemic events and concomitant medication use											X									X
Brief Physical Examination		X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X		X	X	X	X	X	X	X	X	
12 lead ECG[4,6]		X	X	X	X	X	X	X	X								X		X	
Vital Signs[5,6]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Serum Pregnancy Test		X										X	X	X	X	X	X	X	X	
Alcohol & drugs of abuse test		X																		
Haematology[7]		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Clinical Chemistry[7]		X	X	X	X	X	X	X[8]	X			X		X	X	X	X	X	X	
HSV-1 & HSV-2 IgG & IgM[9]		X																		
EBV Viral Load (PCR)[7]		X						X		X		X	X	X	X[10]				X	
EBV Serology - IgG and IgM [7]		X						X		X		X	X	X	X		X		X	
CMV Serology - IgG and IgM[7]		X						X				X	X	X	X		X		X	

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36 month (if applicable) and/or final follow up
PK Blood Sample[6]			X	X	X	X	X	X	X[11]											
CD3 Saturation, free CD3 bound otelixizumab /CD4+/CD8+ Blood Sample[6]			X	X	X	X	X	X	X[11]											
Record insulin usage for 7 days before visit / call		X							X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment			<----------																	---------->
Concomitant Medication Review			<----------																	---------->
Hypoglycaemic / Hyperglycaemic Events			<----------																	---------->
Anti-GAD, anti-IA2, antibody to islet-cell antigen (ICA), anti-ZnT8 & Insulin-antibodies (IAA)		X																		
Anti-otelixizumab antibodies Blood Sample		X												X	X					
Mixed Meal Stimulated C-peptide (MMTT)[12]														X	X[14]		X	X	X[14]	
Beta Cell Function by Hyperglycaemic Clamp[13]		X													X[14]				X[14]	
HbA1c		X													X		X		X	X[15]
Bodyweight		X										X	X	X	X	X	X	X	X	
Various Blood samples for Exploratory Biomarkers		X						X[16]				X		X	X		X		X[17]	
Saliva sample for Pharmacogenetics (PGx)[18]			<----------																	

#Patients will record insulin usage for 7 days prior to out-patient visits (up to Month 24) and before telephone call/visit in Month 36 (if applicable) or final follow up.

Significant AEs including hypoglycaemic (≤3.9 mmol/L; ≤70 mg dL) and hyperglycaemic (>13.9 mmol/L; >250 mg/dL) events will be recorded in a diary whenever they occur, to include start and stop dates.

1. Patient admitted evening of Day -2
2. Discharged on Day 6 if health considered satisfactory by the investigator. Dosing Day 4-6 may be performed on out-patient basis

3. Physical exam performed to monitor for changes in clinical status
4. ECG pre-dose (in triplicate), at the end of the infusion and 6 hours post start infusion (if infusion < 6 hours)
5. Vital signs include temperature, blood pressure and pulse rate (in triplicate), and respiration rate
6. See Section 6.2.3 of the CSP for timings
7. Pre-dose on dosing days
8. If LFTs have shown an upward trend continue to monitor daily after day 6
9. HSV-1 & HSV-2 IgG & IgM will be measured at Day -1 and during the study if clinically indicated
10. If still positive at 6 months EBV viral load will be monitored every 3 months until month 24
11. One sample during visit
12. Blood samples for C-peptide and glucose levels collected at -10, 0, 15, 30, 60, 90 and 120 minutes
13. Plasma C-peptide and glucose levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]
14. Mixed Meal and Glucose Clamp must be separated by at least 4 days
15. Patients will be asked to report verbally their HbA1c at Month 36 (if applicable) and/or final follow-up; followed eventually (if available) by a printed result via regular mail (or scan electronically).
16. Limited biomarkers on Day 6 pre-dose
17. Blood samples for exploratory biomarkers will only be analysed at Month 24 if indicated based on Month 12 results
18. One PGx (DNA) saliva sample taken between Day 1 and 6

11.1.4. Detail for Vitals, ECG and PK & PD Monitoring over the Infusion Period (Cohorts 1-4)

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
1	C1	Dosing																			
		VItals[1,2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X
		ECG	X								X			X							
		PK/CD3 Saturation	X		X	X	X		X		X		X	X							X
	C2-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		ECG	X								X						X				
		PK/CD3 Saturation	X		X	X	X		X		X		X				X				X
2	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X	X	X	X	X	X		X				X
		ECG	X								X										
		PK/CD3 Saturation	X																		
3	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X	X	X	X				X				X
		ECG	X					X			X										
		PK/CD3 Saturation	X																		

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
4	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		X[3]													
		PK/CD3 Saturation	X																		
5	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		X[3]													
		PK/CD3 Saturation	X																		
6	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		X[3]													
		PK/CD3 Saturation	X			X															

1. Blood pressure to be taken in triplicate at Pre-dose
2. Vitals to be repeated at 30 min intervals should there be any safety concern
3. If patients are dosed on an out-patient basis on Day 4, 5 and 6, vital signs and ECGs will stop after the 3 hour post dose time point (if the Investigator is satisfied with the clinical status of the patient), if there are any concerns then vital signs and ECGs may be continued as judged necessary by the investigator until the investigator is satisfied

Day	Cohort	Assessment	Preferably within first hour of visit, time to be recorded in eCRF
14	C1-C4	PK/CD3 Saturation	X

11.2. Appendix 2: Assessment Windows

11.2.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
All	All	Nominal Day	Nominal day – 1 days	Nominal day + 1 days	Visits for Day 14, Day 21 and Week 4 telephone call
All	All	Nominal Day	Nominal day –3 days	Nominal day +3 days	Visits from Week 6 to Month 3
All	All	Nominal Day	Nominal day –7 days	Nominal day +7 days	Visits from Month 6 to Month 24
Safety/PK/CD 3	All	In Window	-5 minutes predose	0 minutes predose	Predose
Safety/PK/CD 3	All	Nominal time point	Nominal time point	+5 minutes	Any postdose up to 6h
Safety/PK/CD 3	All	Nominal time point	Nominal time point	+10 minutes	Any postdose after 6h

Analysis Timepoint will be defined based on the nominal visit label, however a flag will be derived if a visit is considered outside of assessment window. Visits out of window will be included in all analyses but will be flagged in the listings. Sensitivity analyses may be performed excluding these visits.

11.3. Appendix 3: Study Phases

11.3.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to dosing.

Study Phase	Definition
Pre-Treatment	Date < Date of First Dose
During Dosing	Date of First Dose <= Date <= Date of Final Dose + 1.
Post-dose to Week 6	Date of Final Dose + 1 < Date <= Date of Week 6 Visit[1] or Day 42 whichever is greater
Week 6 to Month 24	Date of Week 6 Visit[1] or Day 42 whichever is greater < Date <= Month 24 visit.
Safety Follow-up	Date > Month 24
[1] For participants who were consented Prior to Protocol Amendment 4, Day 42 will be used, as they will not have a Week 6 visit.	

Note: for any rule that is relative to dose, the term date also includes time, if recorded. The end date for a visit as recorded in the SV domain will be used for the determining study phase.

11.3.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and end date is prior to dosing
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Section 11.6 Premature Withdrawals & Handling of Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Ratio to Baseline*	= Post-dose Visit Value / Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 5.2 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- * only generated for strictly >0 parameters.

11.4.2. Reporting Process

Reporting Process	
Software	
• The currently supported versions of SAS will be used to perform all data analyses and generation of displays (tables, figures, and listings).	
Reporting Area (GSK)	
➢ HARP Server	UK1SALX00175
➢ HARP Area	\\arwork\gsk2136525\otx116505\[reporting effort] \\arprod\gsk2136525\otx116505\[reporting effort]
Reporting Area (PXL)	
➢ PXL Server	Kennet
➢ SDTM Data	Transfer folder on Kennet
➢ ADaM Data	Location: [project folder on kennet] /stats/nonversioncontrol/primary/data/sas/derived/main
➢ Programmed TLFs	Location: [project folder on kennet] /stats/nonversioncontrol/primary/output/final
Analysis Datasets	
➢ Analysis datasets will be created according to CDISC / ADaM Standards Library standards. ➢ Define version 2.0 will be used for the SDTM datasets ➢ Define version 2.0 will be used for the analysis datasets.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

11.4.3. Reporting Standards

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.24: 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, unless otherwise stated. • 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 relative to dosing 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 relative to study drug dosing will be shown in listings (Refer to IDSL Compiled Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the participant's listings.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or 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, %
Graphical Displays	
• Refer to IDSL Compiled Statistical Principles 7.01 to 7.13.	

11.5. Appendix 5: Derived and Transformed Data

11.5.1. 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, including the mean. • The nominal time point will be used as described in Section 11.2. • Participants 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 randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Date ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

11.5.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any participant with a missing day will have this imputed as day '15'.
  ○ Any participant 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 at screening (m)^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of doses on Day 1 to Day 6** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly. • In the calculation of daily infusion durations gaps between the two Day 1 syringes are included, i.e. duration will be calculated as end time of infusions – start time of infusions.

11.5.3. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as :

  [1] If QTcB is machine read & QTcF is not provided, then :

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as :

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Adverse Events

General

AE Type	Derivations
AE Onset Time Since First Dose (Days)	➢ If Treatment Start Date > AE Onset Date : **= AE Onset Date - Treatment Start Date** ➢ If Treatment Start Date ≤ AE Onset Date : **= AE Onset Date – Treatment Start Date + 1** ➢ Missing otherwise
AE Duration (Days)	➢ **AE Resolution Date – AE Onset Date + 1**
AE = Drug-related	➢ If relationship is marked 'YES' on eCRF OR value is missing.

Adverse Events : CRS and Clinical Symptoms of Mononucleosis Definition

- The current MedDRA version at time of database lock will be used for coding of AE's.
- AEs considered to be related to CRS during the first 14 days post first dose will be determined by medical expert review conducted by the GSK team.
- For reporting of clinical symptoms of mononucleosis, the following AE's will be extracted based on Preferred Term. In addition, other terms maybe included at the time of reporting.

Reporting	Preferred Term	Verbatim Terms
Clinical	Fatigue	Feeling tired & Low energy

Adverse Events

General

Symptoms of Mononucleosis	Malaise	Feeling unwell
	Myalgia	Joint and muscle pain & Flu like symptoms
	Oropharyngeal pain	Sore throat, throat pain
	Lymphadenopathy	Swollen glands
	Pyrexia	High temperature, Feeling hot and cold & Shivering

Laboratory Parameters

- All BLQ values will be imputed with ½ LLOQ.
- All ALQ values will be imputed with the ALQ + [smallest positive number with the same number of decimal places as the ALQ is reported with]
- Values reported as < x are assumed to have an LLOQ of x.
- Values reported as > x are assumed to have an ALQ of x.

EBV

- EBV Serology:
  - Categories (negative, positive) will be derived from absolute IgG and IgM values according to a worst case approach from absolute virus results

	QUEST Classification of INDEX	Quest classification of U/ml	BDR Classification of AE/mL	Unified Classification
IgG	< OR = 0.90 NEGATIVE 0.91 - 1.09 EQUIVOCAL > OR = 1.10 POSITIVE		negative : <20 positive : 20 or more	NEGATIVE POSITIVE POSITIVE
IgM	< OR = 0.90 NEGATIVE 0.91 - 1.09 EQUIVOCAL > OR = 1.10 POSITIVE	negative: <36 positive: 36 or more	negative : <20 weakly positive : 20-40 positive : 40 or more	NEGATIVE POSITIVE POSITIVE POSITIVE

- EBV Viral Load (EBVPCR_B):
  - Viral Load will also be categorized, using these groups:
    - 0-1000 copies/10^6PBM cells
    - >1000-10000 copies/10^6PBM cells
    - >10000-100000 copies/10^6PBM cells
    - >100000 copies/10^6PBM cells
  - The sames rules as for laboratory parameters will be applied for BLQ/ALQ values.

Any viral load given as > XX.X or < XX.X will be treated in the same manner as described for laboratory parameters. If the result is given as not detected, then it will be imputed as 1 copies/10^6PBM cells instead.

Auto-Antibodies

Positive/Negative results will be derived for all the auto-antibodies, where positive is defined as:

- antibody to glutamic acid decarboxylase (anti-GAD) ≥ 2.6% binding
- antibody to protein tyrosine phosphatase-like protein (anti IA 2) ≥ 0.44% binding
- Qualitative status (positive/negative status) is directly provided for islet cell antigen and will be used
- ZnT8 Autoantibody ≥ 1.02% binding
- IAA ≥ 0.6% binding

In addition, the number of positive results at Screening (with the exception of IAA) will be derived in ADSL.

Immunogenicity

The presence of anti-drug antibodies will be summarized by positive/negative status at each time point. A participant is considered positive at a specific time point if both the Screening and the Confirming sample is positive.

The listing will show individual results for the Screening, Confirming and Titer tests. Not applicable tests will be omitted from the listing.

11.5.4. Efficacy

Weighted Means AUC (MMTT & Hyperglycemic Clamp Test)

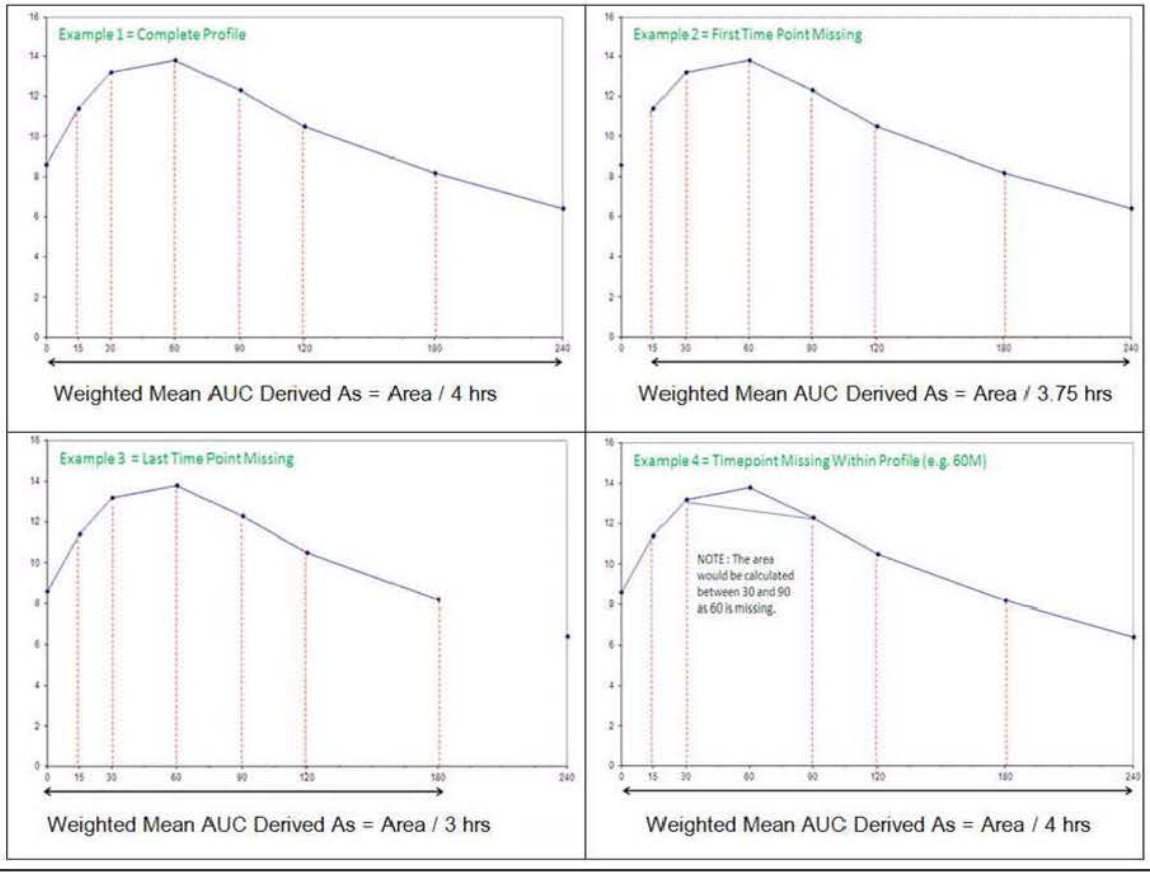
- The weighted mean parameters will be derived by calculating the area under the curve (AUC) using the trapezoidal rule, and then dividing by the actual relevant time interval (i.e. t_f - t_l):

$$\text{Weighted Mean } (t_f\text{-}t_l) = \left[\frac{1}{2}\sum_{i=1}^{I-1}(t_{i+1}-t_i)(y_i+y_{i+1})\right] / [tl - tf]$$

Where (example provided for MMTT AUC(0-120m):

- y_i = Value of endpoint at i^{th} time point
- t_i = The i^{th} actual time point (mins) for MMTT:
  - Before MMTT : t_1=0
  - After MMTT : t_2 =15m, t_3 = 30m, t_4=60m, t_5=90m, t_6=120m
- *tf* = Actual time point (hrs) of first non-missing obs (e.g. in planned time tf=0h)
- *tl* = Actual time point (hrs) of last non-missing obs (e.g. in planned time tl=120m)
- *I* = Number of time points used in the AUC calculation (e.g. I=6)

- The examples provide details of how AUC's are calculated under certain scenario's and is to be adapted based on the study endpoints:



Weighted Means AUC (MMTT & Hyperglycemic Clamp Test)

Profile	Weighted Mean AUC Derivation
Complete	Area / Complete Time Interval
First Time Point Missing	Remaining Area / Remaining Time Interval
Last Time Point Missing	Remaining Area / Remaining Time interval
Time Point Missing Within Profile	Area using values of Remaining Profile / Complete Time Interval

Efficacy

Hyperglycemic Clamp Test: Calculation of Insulin Sensitivity Index (ISI)

- The ISI during the hyperglycemic phase (120-140 min) of the hyperglycemic clamp test (HCT) (Defronzo et al, 1979) will be calculated as:

$$ISI = (M / I)_{120\text{-}140min} \times 100 \quad (a)$$

- Ratio of glucose metabolized between 120 & 140 min (M expressed as $mmol.kg^{-1}.min^{-1}$) **AND** average insulin concentration between 120 & 140 min (I expressed as pmol/l), multiplied by 100.
- As the average insulin concentration is not directly available in the data, it will be replaced with the average C-peptide concentration instead.
- The glucose values taken for the derivation are those measured in the laboratory samples (LBSCAT = CLAMP), not the bedside glucose values (LBSCAT = BEDSIDE GLUCOSE).
- To correct for minor blood glucose fluctuations, M will be calculated as the average glucose infusion rate between 120 and 140 min minus a "space correction".

- Parameter M & I will be derived as follows:

Parameter = M

$$M = INF - SC \quad (b)$$

- M = Amount of glucose metabolized during the last 20 minutes (120-140 min) of the hyperglycemic phase of the HG clamp test.
- M expressed as mmol.kg-1.min-1.
- **INF**: Glucose infusion rate ($mmol.kg^{-1}.min^{-1}$).
- **SC:** Glucose space correction, amount of glucose necessary to fill the plasma glucose equivalent space ($mg.kg^{-1}.min^{-1}$):

$$SC = (G2 - G1) \times 0.095 \quad (c)$$

  - ✓ **G2** and **G1** are the glucose concentrations in milligrams per deciliter at the end and at the beginning of the time period.
  - ✓ The value for **SC** needs to be converted to $mmol.kg^{-1}.min^{-1}$ before filling in **(b).**

Parameter = I

- Average C-peptide concentration during the same period (120-140 min) (expressed as pmol/l).

NOTES:

[1] Following review of the data for missing values, ISI may be calculated using the average C-peptide concentrations instead of average insulin concentrations between 120-140 min.

[2] Following review of the data, HOMA-2IR during HCT at following time points: -180 min (L180), -165 min (L165) and -150 min (L150) and during MMTT at time points: -10 min and 0 min (Matthews et al, 1985; Levy et al, 1998) may be also be calculated.

Efficacy

Mean Daily Insulin Use

- The mean daily insulin use in IU/kg will be derived as follow:

  1. Sum doses by participant and day to get daily dose in IU
  2. Missing daily doses during the seven day space will be imputed with 0
  3. Take the average and divide by the most recent available weight measurement to get mean daily insulin use in IU/kg

Responders (HbA1c)

- A participant will be considered a responder if, at a given visit, the participant has:
  - HbA1c ≤7.0% and
  - Mean daily insulin use < 0.5 units/kg/day.
- HbA1c and mean daily insulin use will be calculated as described above, and values compared at each time point of interest (Week 4, 8, 16, 28, 40, 52 and 64) to determine if a participant is classed as a responder or not

Partial Remission Status

- A participant achieving partial remission status is defined as a participant with Insulin Dose Adjusted A1c (IDAA1C) ≤9.0 [3]
- Insulin-dose adjusted A1c (IDAA1c) is a composite variable, which is a weighted sum of insulin use and HbA1c level.
- IDAA1C is calculated as:
  - HbA1c(%) + 4 x{mean daily insulin use per kg body weight (IU/kg)}
  - where the computation of mean total daily insulin use per kg body weight is as described above
- The calculated IDAA1C value will be rounded to 2 decimal places before assigning partial remission status. Therefore the largest value assigned as ≤9.0 would be 9.004999.

C-peptide Responder

- A participant is considered a C-peptide responder if there is > -40% change from baseline in C-peptide MMTT Weighted Mean AUC at 24 months (so participants with >40% loss in C-peptide are non-responders) [10]
- Participants with missing C-peptide values at 24 months or baseline will have a missing C-peptide responder state. They will be reported as such in frequency tabulations, but not included in figures by C-peptide responder status.
-

11.5.5. Pharmacodynamics

Target Engagement

Overview of CD3 SAT/MOD Target Engagement Parameters

The following parameters will be listed only:

Parameter Category 1	LBTESTCD	LBTEST
CD3 SAT/MOD	CD4	CD4
CD3 SAT/MOD	CD4LY	CD4/Lymphocytes
CD3 SAT/MOD	CD8	CD8
CD3 SAT/MOD	CD8LY	CD8/Lymphocytes
CD3 SAT/MOD	MLYMP	Acquired Lymphocyte Events Mean
CD3 SAT/MOD	CD3EFS1	CD3e Free MESF(CD4+)
CD3 SAT/MOD	CD3EFS2	CD3e Free MESF(CD8+)
CD3 SAT/MOD	CD3EBS1	CD3e Bound MESF(CD4+)
CD3 SAT/MOD	CD3EBS2	CD3e Bound MESF(CD8+)

The following parameters will be summarised:

CD3 SAT/MOD	CD3ER8	CD3e Copies/Cell(CD4+)
CD3 SAT/MOD	CD3ER9	CD3e Copies/Cell(CD8+)
CD3 SAT/MOD	CD3EFR8	CD3e Free Copies/Cell(CD4+)
CD3 SAT/MOD	CD3EFR9	CD3e Free Copies/Cell(CD8+)
CD3 SAT/MOD	CD3EBR8	CD3e Bound Copies/Cell(CD4+)
CD3 SAT/MOD	CD3EBR9	CD3e Bound Copies/Cell(CD8+)

Calculation of Target Engagement (%)

The following formulas will be used to derive the Target Engagement percentage:

$$\text{Total Binding Sites} = \text{Occupied Binding Sites} + \text{Free Binding Sites} + \text{Down Modulated Binding Sites}$$

In this equation, Total Binding Sites is not equal to the corresponding parameter shown above (e.g. CD3ER8 for CD4), except for the Baseline Visit. Instead, they differ by the number of Down Modulated Binding Sites, which is presumed to be zero at Baseline.

As the Total Binding Sites can be assumed to be approximately constant, the number of Down Modulated Binding Sites can be derived as follows:

$$\text{Down Modulated Binding Sites at Visit X} = \text{Total Binding Sites at Baseline} - \text{Total Binding Sites at Visit X}$$

Therefore, percentage Target Engagement can be estimates as follows:

$$\text{Target Engagement (\%)} = \frac{\text{Occupied Binding Sites Visit X} + \text{Down Modulated Binding Sites Visit X}}{\text{Total Binding Sites at Baseline}} \times 100$$

Target Engagement will be derived using 'Copies/Cell'for both CD4 and CD8, but not for MESF values, as the corresponding values have not been measured consistently across cohorts.

Derived Target Engagement (%) Parameters

Parameter Category 1	Parameter Code	Parameter
CD3 SAT/MOD	CD4TE	Otelixizumab Down Modulation and Receptor Occupancy of CD3 ^{unicode epsilon} Target Sites on CD4
CD3 SAT/MOD	CD8TE	Otelixizumab Down Modulation and Receptor Occupancy of CD3 ^{unicode epsilon} Target Sites on CD8

11.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• As defined in the protocol the overall study duration for each participant is 36 months (up to 36 months including the screening period). • Primary study completion for each participant will be at 24 months when all available data will be analysed. • Participant study completion is defined as participants who either prematurely withdrawn or: ○ Patients who had yet to complete their Month 24 visit at the time of approval of Protocol Amendment 9, will be defined as completed if they complete the Month 24 Visit.

Element	Reporting Detail
	• Patients past Month 24 visit at time of approval of Protocol Amendment 9 will be followed up with a final communication or visit (final follow up) and will be defined as completors if they have completed this follow-up visit.Withdrawn participants maybe replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. If data is present after the participants withdrawal from treatment date, this data will be flagged in the listings.

11.6.2. 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 participant 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.6.3. 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. o 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: 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 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. o The AE will then be considered to start on-treatment (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.

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Basophiles	$x10^9$/ L		**0.02**	0.1
Hematocrit	Ratio of 1		0.24	0.54
		Δ from BL	↓0.075	
Hemoglobin	g/dL		8	18
		Δ from BL	↓2.5	
Lymphocytes	$x10^9$/ L		0.8	
Mean Corpuscular Volume (MCV)	fL		80	100
Mean Corpuscular Hemoglobin (MCH)	pg		27	33
Mean Corpuscular Hemoglobin Concentration (MCHC)	g/L		330	360
Monocytes	$x10^9$ / L		0.2	1.0
Eosinophils	$x10^9$ / L			0.44
Neutrophil Count	$x10^9$ / L		1.5	
Platelet Count	$x10^9$ / L		100	550
Red Blood Cell Count (RBC)	$x10^{12}$ / L		4.2	5.9
Reticulocyte Count	$x10^9$ / L		23	90
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	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	umol/L			1.3x ULN
		Δ from BL		↑ 44
Glucose	mmol/L		3	11.1
Potassium	mmol/L		3.2	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	IU/L	High	≥ 2x ULN
			≥ 3x ULN
AST/SGOT	IU/L	High	≥ 2x ULN
Alkaline Phosphatase	IU/L	High	≥ 1.5x ULN
			≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	≥ 1.5xULN T. Bilirubin + ≥ 2x ULN ALT ≥ 2xULN T. Bilirubin + ≥ 3x ULN ALT
Urea Nitrogen (BUN)	mmol/L	Low	< 2.9
		High	>7.1
Chloride	mmol/L	Low	< 98
		High	
		High	≥ 2x ULN
Direct Bilirubin	µmol/L	High	> 7.1
Urate	µmol/L	Low	< 150
		High	> 470
Total Protein	g/L	Low	< 60
		High	> 78

11.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 120
Change from Baseline			
Increase from Baseline QTc	msec	>60	

11.7.3. 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
Respiration Rate	Min^{-1}	< 10	> 30

11.8. Appendix 8: Biomarker Analyses

11.8.1. Handling of duplicate data due to reruns

Due to a rerun of samples from cohorts 1 and 2, duplicate data may be included in the SDTM data. For any such case, only the newer data will be used for summaries and the older data will only be included (with flag) in the listings.

11.8.2. Frequency and phenotype of lymphocyte subsets by flow cytometry

The list of analytes below will be summarised and analysed as per Section 9.4

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
Lymphocytes	LYM	10^9 /L		
CD3	CD3	10^9 /L		CD3 T cells (10^9/L)
CD3/Lymphocytes	CD3LY	%		CD3 T cells
CD4	CD4	10^6 /L		CD4 T cells (10^6/L)
CD4/Lymphocytes	CD4LY	%		CD4 T cells
CD8	CD8	10^6 /L		CD8 T cells (10^6/L)
CD8/Lymphocytes	CD8LY	%		CD8 T cells
CD19	CD19	10^9 /L		B cells (10^9/L)
CD19/Lymphocytes	CD19LY	%		B cells
CD4+CXCR3+CCR6-/CD4+	CDX5554	%		Th1
CD4+CXCR3+CCR6-	CDX555C	10^6 /L	Yes	[CDX5554] x [CD4] / 100
CD4+CXCR3-CCR6-/CD4+	CDX5564	%		Th2
CD4+CXCR3-CCR6-	CDX556C	10^6 /L	Yes	[CDX5564] x [CD4] / 100
CD4+CXCR3-CCR6+/CD4+	CDX5574	%		Th17
CD4+CXCR3-CCR6+	CDX557C	10^6 /L	Yes	[CDX5574] x [CD4] / 100
CD4+CXCR3+CCR6+/CD4+	CDX5584	%		Th1 andTh17
CD4+CXCR3+CCR6+	CDX558C	10^6 /L	Yes	[CDX5584] x [CD4] / 100
CD4+CD25+CD127-/CD4+	CDX5594	%		CD4 Tregs
CD4+CD25+CD127-	CDX559C	10^6 /L	Yes	[CDX5594] x [CD4] / 100
CD8+CXCR3+CCR6-/CD8+	CDX5618	%		Tc1
CD8+CXCR3+CCR6-	CDX561C	10^6 /L	Yes	[CDX5618] x [CD8] / 100
CD8+CXCR3-CCR6-/CD8+	CDX5628	%		Tc2
CD8+CXCR3-CCR6-	CDX562C	10^6 /L	Yes	[CDX5628] x [CD8] / 100
CD8+CXCR3-CCR6+/CD8+	CDX5638	%		Tc17
CD8+CXCR3-CCR6+	CDX563C	10^6 /L	Yes	[CDX5638] x [CD8]) / 100
CD8+CXCR3+CCR6+/CD8+	CDX5648	%		Tc1/ Tc17
CD8+CXCR3+CCR6+	CDX564C	10^6 /L	Yes	[CDX5648] x [CD8] / 100
CD8+CD25+CD127-/CD8+	CDX5668	%		CD8 Tregs
CD8+CD25+CD127-	CDX566C	10 ^6/L	Yes	[CDX5668] x [CD8] / 100
CD8+CD45RA-/CD8+	CDX5118	%		CD8 Memory
CD8+CD45RA+/CD8+	CDX1688	%		CD8 Naive
CD8-CD45RA-/CD8-	CDX601C8	%		CD4 Memory
CD8-CD45RA+/CD8-	CDX602C8	%		CD4 naïve

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
CD8 Memory Exhausted(CD45RA-CD8+)	CDX569J9	%		CD3+CD8+CD45RA-EOMES+ TIGIT+ KLRG1+ (% of CD45RA-CD8+)
CD8 Mem Exhausted IL-6R/CD8 Mem Exhaustd	CDX570K1	%		CD3+CD8+CD45RA-EOMES+ TIGIT+ KLRG1+ CD126+ (% of CD3+CD8+CD45RA-EOMES+ TIGIT+ KLRG1+)
CD8 Mem Exhausted IL-6R MNFI of CD126	CDX570J8	count		CD3+CD8+CD45RA-EOMES+ TIGIT+ KLRG1+ CD126+ (CD126 MFI)
CD3+CD8+CD126+/CD8+	CDX5678	%		CD8 IL-6R
CD3+CD8+CD126+ MNFI of CD126	CDX567J8	count		CD8 IL-6R
CD3+CD8-CD126+/CD8-	CDX568C8	%		CD4 IL-6R
CD3+CD8-CD126+ MNFI of CD126	CDX568J8	count		CD4 IL-6R
CD3+CD8+CD45RA+CD126+ MNFI of CD126	CDX571J8	count		CD8 naive IL-6R
CD3+CD8+CD45RA-CD126+ MNFI of CD126	CDX572J8	count		CD8 memory IL-6R
CD3+CD8-CD45RA+CD126+ MNFI of CD126	CDX573J8	count		CD4 naive IL-6R
CD3+CD8-CD45RA-CD126+ MNFI of CD126	CDX574J8	count		CD4 memory IL-6R

For ADLB PARAMCD will be set to be the same as LBTESTCD and PARAM will be set to LBTEST concatenated with the unit in brackets (in case of counts, no unit will be added).

11.8.3. Percentage of CD3 cells, FoxP3 regulatory cells and TH17 cells by epigenetic quantification

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
CD3+/Total Cells	CD3CE	%		
FoxP3/Total Cells	FOXP3CE	%		
T Helper 17 Cells/Total Cells	TH17CE	%		
FoxP3/CD3+	FOXP3CD3	%	Yes	= [FOXP3CE] x 100/[CD3CE]
T Helper 17 Cells/CD3+	TH17CD3	%	Yes	= [TH17CE] x 100/[CD3CE]

11.8.4. Frequency and phenotype of HLA-A2-resticted antigen-specific CD8+ T cells by multimer analysis

The data for the Frequency and phenotype of HLA-A2-resticted antigen-specific CD8+ T cells by multimer analysis will be reported only for the HLA-A2 Positive population.

Visits where the CD8 count is less 30,000 cells will be excluded from analysis and listed only except for EBV-specific CD8+ T cells for which counts less than 15,000 will be excluded from analysis and listed only. CD8 counts between 30,000 – 50,000 cells will be included in summaries but flagged in listings. Parameters will only be summarised if >40% of baseline visits and >40% of post-baseline visits are evaluable for that parameter.

The list of analytes below are for classification of participants and for determining the quality of cells, and hence will be listed only.

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
Viable Cells Count	VIABCC	Count		
Viable Cells/Total Cells	VIABCCE	%		
CD8+ Count	CD8C	Count		

The list of analytes below will be summarised and analysed as per Section 9.1.1.2.

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
T1D-specific CD8 T Cells/CD8+	T1D8CD8	%		
T1D-specific CD8 T Cells	T1DCD8	10^6/L	Yes	[T1D8CD8]*[CD8] / 100
Insulin B10-18-specific CD8 T Cells/CD8+	B1018C88	%		
Insulin B10-18-specific CD8 T Cells	B1018C8	10^6/L	Yes	[B1018C88] * [CD8] / 100
PPI-specific CD8 T Cells/CD8+	PPICD88	%		
PPI-specific CD8 T Cells	PPICD8	10^6/L	Yes	[PPICD88] * [CD8] / 100
Novel Insulin Epitope CD8 T Cells/CD8+	NINECD88	%		
Novel Insulin Epitope CD8 T Cells	NINECD8	10^6/L	Yes	[NINECD88] * [CD8] / 100
GAD65-specific CD8 T Cells/CD8+	GD65CD88	%		
GAD65-specific CD8 T Cells	GD65CD8	10^6/L	Yes	[GD65CD88] * [CD8] / 100
IGRP-specific CD8 T Cells/CD8+	IGRPCD88	%		
IGRP-specific CD8 T Cells	IGRPCD8	10^6/L	Yes	[IGRPCD88] * [CD8] / 100
IA2-specific CD8 T Cells/CD8+	IA2CD88	%		
IA2-specific CD8 T Cells	IA2CD8	10^6/L	Yes	[IA2CD88] * [CD8] / 100

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
ppIAPP-specific CD8 T Cells/CD8+	PIAPCD88	%		
ppIAPP-specific CD8 T Cells	PIAPCD8	10^6/L	Yes	[PIAPCD88] * [CD8] / 100
ZnT8-specific CD8 T Cells/CD8+	ZNT8CD88	%		
ZnT8-specific CD8 T Cells	ZNT8CD8	10^6/L	Yes	[ZNT8CD88] * [CD8] / 100
A2-specific CD8 T Cells/CD8+	A2CD8CD8	%		
A2-specific CD8 T Cells	A2CD8	10^6/L	Yes	[A2CD8CD8] * [CD8] / 100
EBV-specific CD8 T Cells/CD8+	EBVCD88	%		
EBV-specific CD8 T Cells	EBVCD8	10^6/L	Yes	[EBVCD88] * [CD8] / 100
CXCR3+ T1D-specific CD8 T Cells/CD8+	CDX5388	%		Migratory T1D-specific cells/ total CD8 cells
CXCR3+ T1D-specific CD8 T Cells	CDX538C	10^6/L	Yes	[CDX5388] * [CD8] / 100
CCR7+CD45RA+ T1D CD8+ Cells/T1D CD8	CDX543J6	%		Naive T1D-specific cells / total T1D-specific cells
CCR7+CD45RA+ T1D CD8 T Cells	CDX543C	10^6/L	Yes	[CDX543J6] * [T1DCD8] / 100
CCR7+CD45RA- T1D CD8+ Cells/T1D CD8	CDX544J6	%		Central memory T1D-specific cells / total T1D-specific cells
CCR7+CD45RA- T1D CD8 T Cells	CDX544C	10^6/L	Yes	[CDX544J6] * [T1DCD8] / 100
CCR7-CD45RA- T1D CD8+ Cells/T1D CD8	CDX545J6	%		Effector T1D-specific cells / total T1D-specific cells
CCR7-CD45RA- T1D CD8+ T Cells	CDX545C	10^6/L	Yes	[CDX545J6] * [T1DCD8] / 100
CCR7-CD45RA+ T1D CD8+ Cells/T1D CD8	CDX546J6	%		Terminally differentiated effector memory T1D-specific cells / total T1D-specific cells
CCR7-CD45RA+ T1D CD8 T Cells	CDX546C	10^6/L	Yes	[CDX546J6] * [T1DCD8] / 100
CCR7+CD45RA+CXCR3+T1D CD8 T Cell/T1D CD8	CDX539J6	%		Migratory Naive T1D-specific cells / total T1D-specific cells
CCR7+ CD45RA+ CXCR3+T1D CD8 T Cell	CDX539C	10^6/L	Yes	[CDX539J6] * [T1DCD8] / 100
CCR7+CD45RA-CXCR3+ T1D CD8+ Cell/T1D CD8	CDX540J6	%		Migratory Central memory T1D-specific cells / total T1D-specific cells
CCR7+CD45RA-CXCR3+ T1D CD8 T Cells	CDX540C	10^6/L	Yes	[CDX540J6] * [T1DCD8] / 100
CCR7-CD45RA-CXCR3+ T1D CD8+ Cell/T1D CD8	CDX541J6	%		Migratory Effector T1D-specific cells / total T1D-specific cells
CCR7-CD45RA-CXCR3+ T1D CD8 T Cells	CDX541C	10^6/L	Yes	[CDX541J6] * [T1DCD8] / 100
CCR7-CD45RA+CXCR3+ T1D CD8+ Cell/T1D CD8	CDX542J6	%		Migratory Terminally differentiated effector memory T1D-specific cells / total T1D-specific cells
CCR7-CD45RA+CXCR3+	CDX542C	10^6/L	Yes	[CDX542J6] * [T1DCD8] / 100

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
T1D CD8 T Cells				
CCR7+CD45RA+ EBV CD8+ Cells/EBV CD8	CDX551J7	%		Naive EBV -specific cells / total EBV-specific cells
CCR7+CD45RA+ EBV CD8 T Cells	CDX551C	10^6/L	Yes	[CDX551J7] * [EBVCD8] / 100
CCR7+CD45RA- EBV CD8+ Cells/EBV CD8	CDX552J7	%		Central memory EBV-specific cells / total EBV-specific cells
CCR7+CD45RA- EBV CD8 T Cells	CDX552C	10^6/L	Yes	[CDX552J7] * [EBVCD8] / 100
CCR7-CD45RA-EBV CD8+ Cells/EBV CD8	CDX553J7	%		Effector EBV-specific cells / total EBV-specific cells
CCR7-CD45RA-EBV CD8 T Cells	CDX553C	10^6/L	Yes	[CDX553J7] * [EBVCD8] / 100
CCR7-CD45RA+ EBV CD8+ Cells/EBV CD8	CDX554J7	%		Terminally differentiated effector memory EBV-specific cells / total EBV-specific cells
CCR7-CD45RA+ EBV CD8 T Cells	CDX554C	10^6/L	Yes	[CDX554J7] * [EBVCD8] / 100
CCR7+CD45RA+CXCR3+ EBV CD8+ Cell/EBV CD8	CDX546J7	%		Migratory Naive EBV-specific cells / total EBV-specific cells
CCR7+CD45RA+CXCR3+ EBV CD8 T Cells	CDX547C	10^6/L	Yes	[CDX546J7] * [EBVCD8] / 100
CCR7+CD45RA-CXCR3+ EBV CD8+ Cell/EBV CD8	CDX548J7	%		Migratory Central memory EBV-specific cells / total EBV-specific cells
CCR7+CD45RA-CXCR3+ EBV CD8 T Cells	CDX548C	10^6/L	Yes	[CDX548J7] * [EBVCD8] / 100
CCR7-CD45RA-CXCR3+ EBV CD8+ Cell/EBV CD8	CDX549J7	%		Migratory Effector EBV-specific cells / total EBV-specific cells
CCR7-CD45RA-CXCR3+EBV CD8 T Cell	CDX549C	10^6/L	Yes	[CDX549J7] * [EBVCD8] / 100
CCR7-CD45RA+CXCR3+ EBV CD8+ Cell/EBV CD8	CDX550J7	%		Migratory Terminally differentiated effector memory EBV-specific cells / total EBV-specific cells
CCR7-CD45RA+CXCR3+ EBV CD8 T Cells	CDX550C	10^6/L	Yes	[CDX550J7] * [EBVCD8] / 100

11.8.5. Frequency of interferon-gamma- secreting antigen-reactive cells by ELISPOT

The list of analytes below are for classification of participants and for determining the quality of cells, and hence will be listed only.

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
Viable Cells Count	VIABCC	Count		
Viable Cells/Total Cells	VIABCCE	%		

The list of analytes below will listed. PARAM/PARAMCD will be created from LBTEST/LBTESTCD and the stimulus (e.g. EBV) which is stored in SUPPLB.

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
Interferon Gamma Spot Forming Cell Count	IFNGSFCC	count/10^6PBMC		

The following stimulants have been used:

- Unstimulated
- GAD – Glutamic Acid Decarboxylase
- icIA-2 – Intracellular Islet Antigen-2
- EBV – Epstein Barr Virus
- PI – Pro-insulin
- PI C-pep – Pro-insulin-derived C-peptide
- PPI Leader – Prepro-insulin Leader

11.8.6. Quantification of serum cytokines and soluble cytokine receptors

The list of analytes below will be summarised and analysed as per Section 9.4.

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
Interferon Gamma (ng/L)	IFNG	(ng/L)		
Soluble Interleukin 6 Receptor (ng/mL)	IL6SR	(ng/mL)		
Interleukin 6 Signal Transducer (ng/mL)	IL6ST	(ng/mL)		Soluble gp130
Interleukin 10 (ng/L)	INTLK10	(ng/L)		
Interleukin 12 (ng/L)	INTLK12	(ng/L)		
Interleukin 13 (ng/L)	INTLK13	(ng/L)		
Interleukin 1 Beta (ng/L)	INTLK1B	(ng/L)		
Interleukin 2 (ng/L)	INTLK2	(ng/L)		
Interleukin 4 (ng/L)	INTLK4	(ng/L)		
Interleukin 6 (ng/L)	INTLK6	(ng/L)		
Interleukin 8 (ng/L)	INTLK8	(ng/L)		

11.8.7. TCR deep sequencing

The list of analytes below will be summarised and analysed as per Section 9.1.1.2.

Test (PFTEST)	Test Code (PFTESTCD)	Units	Derived	Details
Productive Clonality	AH001	%		

Further TCR deep sequencing endpoint may be explored through Adaptive Biotechnology's ImmunoSeq™ Analyser but these are considered as further exploratory work outside of this RAP.

11.8.8. Suppressive activity of regulatory cells

The list of analytes below will be listed only. PARAM/PARAMCD will be created from LBTEST/LBTESTCD and the Stimulus (Treg:Teff) an Stimulus concentrations (e.g. 0:1) which are stored in SUPPLB.

Lab Test (LBTEST)	Lab Test Code (LBTESTCD)	Units	Derived	Details
Count	COUNT	CPM		
Percentage suppression	PCTSUPP	%		

The following stimulus will be used (stored in SUPPLB):

- Treg:Teff

The following stimulus concentrations will be used (stored in SUPPLB):

- 0:1
- 1:1
- 1:2
- 1:4

11.8.9. Number of digits for display of biomarker data

To ensure that the outputs are readable, if the maximum value of the derived variable in the units given in this RAP is < 0.0001 both unit and values may be multiplied with 10^3n (n being an integer) so that the maximum value is ≥ 0.0001.

Otherwise, the following rules will apply:

- All individual continuous and count data will be displayed with three significant digits. Summary statistics will follow the normal IDSL rules, e.g. the mean will be presented with four significant digits.
- The display of percentages variable will depend on the median percentage across all treatments and time points, in the following manner:
    - The number of decimal points will be chosen so that the median as an individual value would be presented with three significant digits (e.g. if the median 20.5% all individual percentages should be displayed with one decimal place).
    - Normal rules for derived summary statistics apply.
    - Any percentage larger than zero which would be displayed as zero according to the above rules will instead be displayed as "<X", where X is the smallest non-zero percentage that can be displayed.

11.9. Appendix 9: Abbreviations & Trademarks

11.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRS	Cytokine Release Syndrome
CS	Clinical Statistics
CSR	Clinical Study Report
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
EBV	Epstein-Barr virus
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
INS	Insulin
IP	Investigational Product
ITT	Intent-To-Treat
MMTT	Mixed Meal Tolerance Test
MMRM	Mixed Model Repeated Measures
PBMC	Peripheral Blood Mononuclear Cells
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
ULQ	Upper Limit of quantification

Abbreviation	Description
ULN	Upper Limit of Normal

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
SAS/STAT
WinNonlin
Spotfire

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.XX	N/A
Safety	2.01 to 2.XX	2.01 to 2.XX
Efficacy	3.01 to 3.XX	3.01 to 3.XX
Pharmacodynamic	4.01 to 4.XX	4.01 to 4.XX
Biomarker	5.01 to 5.XX	5.01 to 5.XX
Pharmacokinetic	6.01 to 6.XX	6.01 to 6.XX
Section	**Listings**	
ICH Listings	1 to XX	
Other Listings	XX+1 to ZZ	

11.10.2. 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
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Pharmacodynamic	PD_Fn	PD_Tn	PD_Ln
Biomarker	BIO_Fn	BIO_Tn	BIO_Ln
Listings			OTHER_Ln

NOTES:

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

11.10.3. Deliverable [Priority]

The details provide abbreviations for the 'Delivery Priority' for the various reporting efforts for which displays will be generated.

Abbreviation	Reporting Effort
FA (SAC)	Final Analysis Statistical Analysis Complete

11.10.4. 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 for the Subject Conclusion Record	Programmer to update primary reason for withdrawal to be study specific.	FA (SAC)
1.02.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		FA (SAC)
1.03.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		FA (SAC)
1.04.	Enrolled	SP1	Summary of Study Populations		FA (SAC)
1.05.	Safety	DV1	Summary of Important Protocol Deviations	Generated, if data permits. As required, refer to PDMP.	FA (SAC)
1.06.	Safety	SP3	Summary of Exclusions from Per Protocol Population		FA (SAC)
1.07.	Safety	IE1	Summary of Inclusion / Exclusion Criteria Deviations		FA (SAC)
Demographics					
1.08.	Safety	DM1, DM5, DM 11	Summary of Demographic Characteristics, Race and Racial Combinations and Age Ranges	Please combine shells in order DM1, DM5, DM 11. In addition those items please also add the categories for number of positive antibodies at screening (see Section 11.5.3)	FA (SAC)
Medical Conditions					

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.09.	Safety	MH4	Summary of Past and Current Medical Conditions	We only have current conditions, so need to display only those	FA (SAC)
Concomitant Medications					
1.10.	Safety	CM7	Summary of Concomitant Medications	Split as described in Section 11.3	FA (SAC)
Exposure					
1.11.	Safety	EX1	Summary of Exposure to Study Drug	Also include daily infusion duration in hours for each dosing day	FA (SAC)

11.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
AE					
2.01.	Safety	AE13	Adverse Event Overview	Split as described in Section 11.3	FA (SAC)
2.02.	Safety	AE15	Summary of All Adverse Events by System Organ Class and Preferred Term	Split as described in Section 11.3 Add a "Any Event" category for each SOC even if not in shell	FA (SAC)
2.03.	Safety	AE15	Summary of Drug-Related Adverse Events	Split as described in Section 11.3 Add a "Any Event" category for each SOC even if not in shell	FA (SAC)
2.04.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term	Split as described in Section 11.3	FA (SAC)
2.05.	Safety	AE1	Summary of AEs Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Do not split this output by phase	FA (SAC)
2.06.	Safety	AE5	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term	Split as described in Section 11.3	FA (SAC)
2.07.	Safety	AE5	Summary of Drug-Related Adverse Events by Maximum Grade by System Organ Class and Preferred Term	Split as described in Section 11.3	FA (SAC)
Cytokine Release Syndrome					

2.08.	Safety	AE15	Summary of Adverse Events - Cytokine Release Syndrome Induced Symptoms	• Definition of Cytokine Release Syndrome in Section 11.5.3 • Overall only, not split by study phase.	FA (SAC)
Epstein-Barr Virus					
2.09.	Safety	AE15	Summary of Adverse Events Considered to be Potentially Associated with EBV Reactivation	• Clinical Symptoms of Mononucleosis AE Terms to include are in Section 11.5.3 • Overall only not split by study phase.	FA (SAC)
2.10.	Safety	Non-Standard SAFE_T3	Summary of categorical values of Epstein-Barr Virus (Serology: IgG & IgM)	• Categories (negative, positive) to be derived from absolute values according to a worst case approach as described in Section 11.5.3	FA (SAC)
2.11.	Safety	Non-Standard SAFE_T2	Summary of Epstein-Barr Viral Load (PCR)	• Geometric Means	FA (SAC)
2.12.	Safety	Non-Standard SAFE_T4	Categorical Summary of Epstein-Barr Viral Load (PCR)		FA (SAC)
Labs					

2.13.	Safety	LB1	Summary of Laboratory Values	• Order parameters alphabetically. • BY Labtype (1. Chemistry, 2. Haematology)	FA (SAC)
2.14.	Safety	LB1	Summary of Laboratory Changes from Baseline	• Order parameters alphabetically • BY Labtype (1. Chemistry, 2. Haematology)	FA (SAC)
2.15.	Safety	LB15	Summary of Worst Case Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline	• Order parameters alphabetically • BY Labtype (1. Chemistry, 2. Haematology)	FA (SAC)
Electrocardiograms					
2.16.	Safety	EG1	Summary of ECG Findings		FA (SAC)
2.17.	Safety	EG2	Summary of Change from Baseline in ECG Values		FA (SAC)
2.18.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		FA (SAC)
2.19.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		FA (SAC)
Vital Signs					
2.20.	Safety	VS1	Summary of Change from Baseline in Vital Signs		FA (SAC)
2.21.	Safety	VS7	Summary of Worst Case Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		FA (SAC)

Immunogenicity					
2.22.	Safety	Non-Standard EFF_T4	Summary of Immunogenicity	• With positive instead of responder	FA (SAC)

11.10.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL No. / E.G. Shell**	**Title**	**Programming Notes**	**Delivery Priority**
Labs					
2.01	Safety	SAF_F1	Individual Subject Plot - Hematology & Clinical Chemistry Selected Parameters		FA (SAC)
Epstein-Barr Virus Viral Load					
2.02	Safety	EFF_F2 (with different error bars, see notes)	Geometric Mean (+/- CV%): Epstein-Barr Virus Viral Load	• X-axis: time • Y-Axis: Geometric Mean Load (semi-log) • Show error bars at (1+CV%) * GeoMean and GeoMean/(1+CV%) • Line by group	FA (SAC)

11.10.7. Efficacy Tables

Efficacy : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Mixed Meal Tolerance Test : Weighted Mean AUC(0-120 mins) C-Peptide & Glucose					
3.01.	ITT (Treated)	Non-Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline) : C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test		FA (SAC)
3.02.	ITT (Treated)	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test	• Include related estimated LSMeans and treatment differences.	FA (SAC)
3.03.	Fully Treated	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test	• Include related estimated LSMeans and treatment differences.	FA (SAC)
Clamp (Hyperglycaemic Phase) : Weighted Mean AUC(60-140) C-Peptide & Glucose					

3.04.	ITT (Treated)	Non-Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline) : C-Peptide and Glucose Weighted Mean AUCs (60-140 mins) from Hyperglycemic Clamp Test		FA (SAC)
3.05.	ITT (Treated)	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide and Glucose Weighted Mean AUCs (60-140 mins) from Hyperglycemic Clamp Test	• Include related estimated LSMeans and treatment differences.	FA (SAC)
3.06.	Fully Treated	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide and Glucose Weighted Mean AUCs (60-140 mins) from Hyperglycemic Clamp Test	• Include related estimated LSMeans and treatment differences.	FA (SAC)
CLAMP (Insulin Sensitivity Index)					
3.07.	ITT (Treated)	Non-Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline) : Insulin Sensitivity Index from Hyperglycemic Clamp Test		FA (SAC)
3.08.	ITT (Treated)	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline : Insulin Sensitivity Index from Hyperglycemic Clamp Test	Include related estimated LSMeans and treatment differences.	FA (SAC)
Mean Daily Insulin Use					
3.09.	ITT (Treated)	Non-Standard EFF_T1	Summary Statistics: (Absolute, Change from Baseline and Percentage Change from Baseline) : Mean Daily Insulin Use	• Please add percentage change from baseline to the shell (as BY)	FA (SAC)
3.10.	ITT (Treated)	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline : Mean Daily Insulin Use	Include related estimated LSMeans and treatment differences.	FA (SAC)
%HbA1c					

3.11.	ITT (Treated)	Non-Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline) : %HbA1c		FA (SAC)
3.12.	ITT (Treated)	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline: %HbA1c	Include related estimated LSMeans and treatment differences.	FA (SAC)
Body Weight					
3.13.	ITT (Treated)	Non-Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline) : Body Weight		FA (SAC)
3.14.	ITT (Treated)	Non-Standard EFF_T2	Summary of Statistical Analysis (MMRM) Results of Change from Baseline: Body Weight	Include related estimated LSMeans and treatment differences.	FA (SAC)
Hypoglycemic & Hyperglycemic Events					
3.15.	ITT (Treated)	Non-Standard EFF_T3	Summary of Hypoglycaemic & Hyperglycaemic Events by Intensity, SAE Status, Relationship to Investigational Product and Withdrawal Status		FA (SAC)
Responder Status					
3.16.	ITT (Treated)	Non-Standard EFF_T4	Number and Percent of Subjects Meeting Definition of Glycemic Responder	Include Partial Remission Status and Hba1c responder status	FA (SAC)
3.17.	ITT (Treated)	Non-Standard EFF_T4	Number and Percent of Subjects Meeting Definition of C-Peptide Responder		FA (SAC)

11.10.8. Efficacy Figures

Efficacy Figures					
No.	**Population**	**IDSL No. / E.G. Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
Mixed Meal Tolerance Test : Weighted Mean AUC(0-120 mins) C-Peptide & Glucose					
3.01	ITT (Treated)	Non- Standard EFF_F1	Model Adjusted Mean (+/- SE) Change from Baseline Plot : C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test	By : Parameter X-Axis : Continuous scale for visit (months) Y-Axis : Mean (+/- SD) Chg from BL : Continuous scale for visit (moths) Legend : Treatment	FA (SAC)
Clamp (Hyperglycaemic Phase) : Weighted Mean AUCs (60-140 & 0-140 mins) C-Peptide & Glucose					
3.02	ITT (Treated)	Non- Standard EFF_F1	Model Adjusted Mean (+/- SE) Change from Baseline Plot : C-Peptide Weighted Mean AUCs (60-140 mins) from Hyperglycaemic Clamp Test	As Figure 3.01, adapted accordingly to the data	FA (SAC)
Mean Daily Insulin Use					
3.03	ITT (Treated)	Non-Standard EFF_F1	Model Adjusted Mean (+/- SE) Change from Baseline Plot : Mean Daily Insulin Use	As Figure 3.01, adapted accordingly to the data	FA (SAC)
%HbA1c					
3.04	ITT (Treated)	Non- Standard EFF_F1	Model Adjusted Mean (+/- SE) Change from Baseline Plot : %HbA1c	As Figure 3.01, adapted accordingly to the data	FA (SAC)
Hyperglycemic and hypoglycemic events by month					

Efficacy Figures					
No.	**Population**	**IDSL No. / E.G. Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
3.05	ITT (Treated)	EFF_F2	Mean (+/- SE) Number of hyperglycemic and hypoglycemic events by month		FA (SAC)

11.10.9. Pharmacodynamic Tables

Pharmacodynamic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic					
4.01.	Safety	Non- Standard PD_T1	Summary Statistics (Absolute and Change from Baseline): Target Engagement	For parameters with imputation please also include no. of subjects with LLQs & ULQ. Include the parameters to be summarized from 11.5.5 and also show the two derived % Target Engagement variables	FA (SAC)

11.10.10. Pharmacodynamic Figures

Pharmacodynamic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic					
4.01.	Fully Treated	Non- Standard EFF_F1	Mean (+/- SE) Change from Baseline in Target Engagement	Pages BY parameters, same as table. Lines by group. Please show same parameters as in Table 4.01.	FA (SAC)

11.10.11. Biomarker Tables

Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarker					
5.01.	Fully Treated	Non- Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline): Frequency and phenotype of lymphocyte subsets by flow cytometry		FA (SAC)
5.02.	Fully Treated	EFF_T5	Summary Statistics (Absolute and Change from Baseline): Frequency and phenotype of lymphocyte subsets by flow cytometry by C-Peptide Response		FA (SAC)
5.03.	Multimer Analyses	Non- Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline): Frequency and phenotype of HLA-A2-resticted EBV-specific CD8+ T cells by multimer analysis		FA (SAC)
5.04.	Fully Treated	Non- Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline): Quantification of serum cytokines and soluble cytokine receptors		FA (SAC)
5.05.	Fully Treated	Non- Standard EFF_T1	Summary Statistics (Absolute and Change from Baseline): TCR deep sequencing		FA (SAC)

11.10.12. Biomarker Figures

Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarker					
5.01.	Fully Treated	EFF_F3	Mean (+/- SE) Change from Baseline in Frequency and phenotype of lymphocyte subsets by flow cytometry by C-Peptide Response		FA (SAC)

11.10.13. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
6.01	Fully Treated	PK01	Summary of Free Serum Otelixizumab Concentration-Time Data by Treatment		FA (SAC)

11.10.14. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
6.01	Fully Treated	PK16a	Individual Free Serum Otelixizumab Concentration-Time Plots (Linear and Semi-Log) by Subject		FA (SAC)
6.02	Fully Treated	PK17	Mean Free Serum Otelixizumab Concentration-Time Plots by Treatment (Linear and Semi-Log)	Use geometric mean for semi-log scale	FA (SAC)
6.03	Fully Treated	PK18	Median Free Serum Otelixizumab Concentration-Time Plots by Treatment (Linear and Semi-Log)		FA (SAC)

11.10.15. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
01.	Randomised	TA1	Listing of Randomised and Actual Treatments		FA (SAC)
Subject Disposition					
02.	Enrolled	ES2	Listing of Reasons for Study Withdrawal		FA (SAC)
03.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		FA (SAC)
04.	Enrolled	DV2	Listing of Important Protocol Deviations		FA (SAC)
05.	Enrolled	SP3	Listing of Exclusions from Any Population		FA (SAC)
06.	Screened	ES7	Listing of Reason for Screen Failure		FA (SAC)
07.	Enrolled	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		FA (SAC)
Exposure					
08.	Safety	EX3	Listing of Exposure Data	• List each infusion, we will give duration in minutes (end of infusion – start of infusion). • We can omit Dosing Frequency.	FA (SAC)
Demographics					
09.	Safety	DM2	Listing of Demographic Characteristics		FA (SAC)
10.	Safety	DM9	Listing of Race		FA (SAC)

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	Safety	Non-Standard OTHER_L10	Listing of Family History of Cardiovascular Risk		FA (SAC)
12.	Safety	Non-Standard OTHER_L11	Listing of Substance Use		FA (SAC)
Conmeds					
13.	Safety	CM3	Listing of Concomitant Medications	Include ATC/Ingredient	FA (SAC)
14.	Safety	Non-Standard OTHER_L6	Listing of Insulin Use	• CMCAT = DAILY INSULIN USE	FA (SAC)
AE					
15.	Safety	AE8	Listing of All Adverse Events		FA (SAC)
16.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		FA (SAC)
17.	Safety	AE8CPA	Listing of Serious Adverse Events		FA (SAC)
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		FA (SAC)
19.	Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		FA (SAC)
20.	Safety	AE2	Relationship of Adverse Event SOCs, PTs, and Verbatim Text		FA (SAC)
21.	Safety	AE8	Listing of All Adverse Events - Cytokine Release Syndrome Induced Symptoms	• See Section 11.5.3 for definition	FA (SAC)

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	Safety	AE8	Listing of All Adverse Events – Considered Potentially Associated with EBV Reactivation	• See Section 11.5.3 for definition	FA (SAC)
23.	Safety	OTHER_L12	Listing of Epstein-Barr Virus Serology: IgG & IgM and Viral Load: PCR	Please include the following: EBCIGGAS, EBVMSOS, EBCIGGAB, EBVMABZ, EBCIGMAB, EBVDNA	FA (SAC)
LABS					
24.	Safety	LB5	Listing of All Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance		FA (SAC)
25.	Safety	LB14	Listing of Haematology Laboratory Data with Character Results		FA (SAC)
26.	Safety	LB5	Listing of All Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance		FA (SAC)
27.	Safety	LB14	Listing of Clinical Chemistry Laboratory Data with Character Results		FA (SAC)
28.	Safety	LB5	Listing of All Serology Data		FA (SAC)
29.	Safety	LB14	Listing of Serology Data with Character Results		FA (SAC)
ECG's					
30.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		FA (SAC)
31.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	Including change from Baseline	FA (SAC)

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
32.	Safety	EG5	Listing of Abnormal ECG Findings		FA (SAC)
Vital Signs					
33.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance		FA (SAC)
34.	Safety	VS4	Listing of All Vital Signs for Subjects with Values of Potential Clinical Importance		FA (SAC)
Pharmacokinetics					
35.	Safety	PK07	Listing of free serum concentration-Time Data		FA (SAC)

11.10.16. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population, Safety and Efficacy					
36.	Safety	CP_ML1 p	Listing of Dosing Times, Meal Start and End Times on Fed Treatment Days	Classify as Safety for HARP/SAFIRE	FA (SAC)
37.	Safety	Non-Standard Other_L4	Listing of Auto-Antibody Results	Classify as Study Population for HARP/SAFIRE	FA (SAC)
38.	Safety	Non-Standard Other_L3	Listing of Immunogenicity Results	Classify as Safety for HARP/SAFIRE	FA (SAC)
39.	Safety	Non-Standard Other_L1	Listing of C-Peptide & Glucose from Mixed Meal Test	• List by Parameter • Absolute and change from baseline result to be presented.	FA (SAC)
40.	Safety	Non-Standard Other_L2	Listing of C-Peptide & Glucose from Mixed Meal Test: Derived Parameters	• List by Parameter • Absolute and change from baseline result to be presented. • Also include C-peptide response	FA (SAC)
41.	Safety	Non-Standard Other_L8	Listing of C-Peptide & Glucose from Clamp	• List by Parameter • Absolute and change from baseline result to be presented.	FA (SAC)

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
42.	Safety	Non-Standard Other_L9	Listing of C-Peptide & Glucose from Clamp : Derived Parameters	○ List by Parameter ○ Absolute and change from baseline result to be presented.	FA (SAC)
43.	Safety	Non-Standard Other_L1	Listing of Insulin Sensitivity Index (Hyperglycemic Clamp), Mean Daily Insulin Usage and %HbA1c	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint. • Include glycemic response variables	FA (SAC)
44.	Safety	Non-Standard Other_L5	Listing of Hypoglycemic & Hyperglycemic Event Rates		FA (SAC)
45.	Safety	Non-Standard Other_L7	Cardiovascular Events	Classify as Safety for HARP/SAFIRE	FA (SAC)
Pharmacodynamics					
46.	Safety	Non-Standard Other_L1	Listing of Pharmacodynamics including Target Engagement	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
Biomarkers					

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
47.	ITT (Treated)	Non-Standard Other_L1	Listing of frequency and phenotype of lymphocyte subsets by flow cytometry	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
48.	ITT (Treated)	Non-Standard Other_L1	Listing of frequency of FoxP3 regulatory cells and TH17 cells by epigenetic quantification	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
49.	Multimer Analyses	Non-Standard Other_L1	Listing of frequency and phenotype of HLA-A2-resticted antigen-specific CD8+ T cells by multimer analysis	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
50.	ITT (Treated)	Non-Standard Other_L1	Listing of frequency of interferon-gamma-secreting antigen-reactive cells by ELISPOT	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
51.	ITT (Treated)	Non-Standard Other_L1	Listing of quantification of serum cytokines and soluble cytokine receptors	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
52.	ITT (Treated)	Non-Standard Other_L1	Listing of TCR deep sequencing results	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
53.	ITT (Treated)	Non-Standard Other_L1	Listing of suppressive activity of regulatory cells	• Absolute and change from baseline result to be presented. • Example Other_L1 modified based on endpoint.	FA (SAC)
Statistical Listings					
54.	ITT (Treated)	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots • Also include a listing showing the p-values for the model selection approach described in Section 9.1.5.1 in the following format: Covariate Type III P-value BMI 0.XXXXX (from 1) BMI*trt 0.XXXXX (from 2) Show this for each covariate, but do not include tests for the other variables in the model	FA (SAC)
55.	ITT (Treated)	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide Weighted Mean AUCs (60-140 mins) from Hyperglycemic Clamp Test	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	FA (SAC)

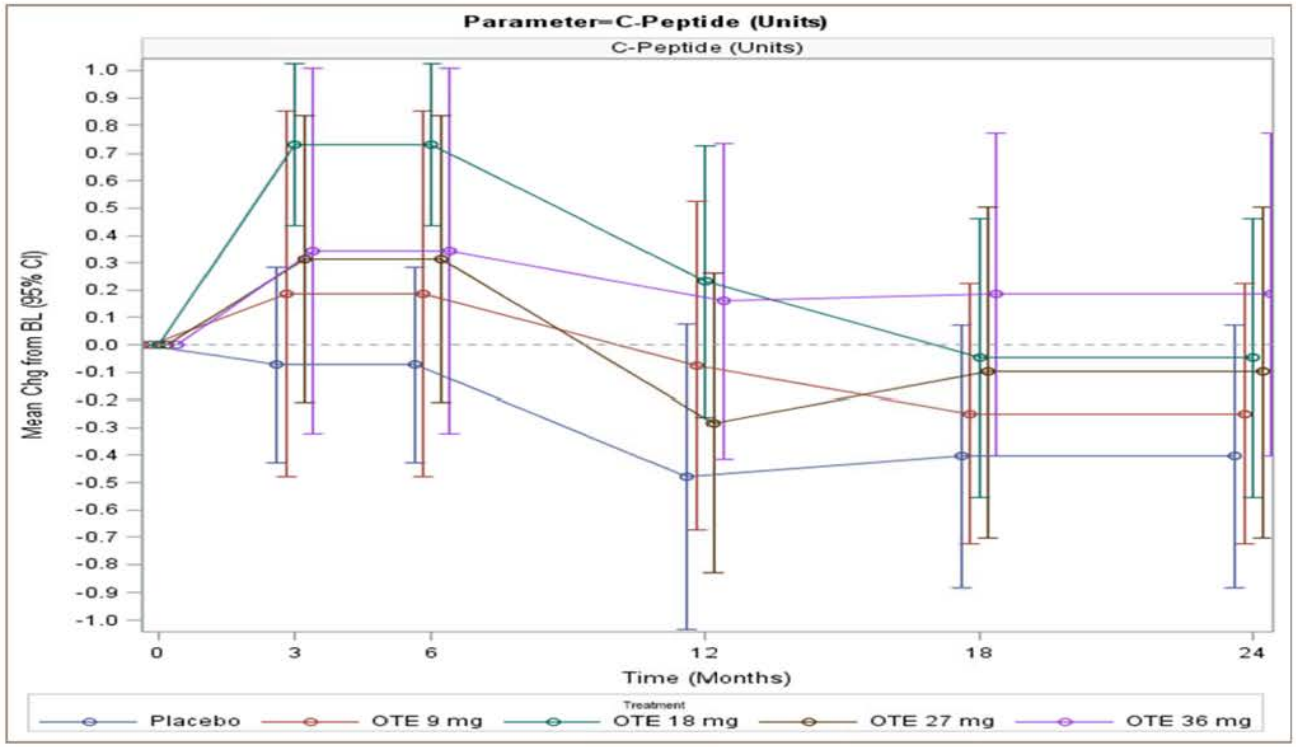
Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
56.	Fully Treated	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	FA (SAC)
57.	Fully Treated	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline : C-Peptide Weighted Mean AUCs (60-140 mins) from Hyperglycemic Clamp Test	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	FA (SAC)
58.	ITT (Treated)	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline : Insulin Sensitivity Index from Hyperglycemic Clamp Test	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	FA (SAC)
59.	ITT (Treated)	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline : Mean Daily Insulin Use	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	FA (SAC)
60.	ITT (Treated)	SAS Output	Statistical Output for Statistical Analysis (MMRM) Results of Change from Baseline: %HbA1c	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	
61.	ITT (Treated)	SAS Output	Summary of Statistical Analysis (MMRM) Results of Change from Baseline: Body Weight	• Please include standard SAS output, including estimation of variance components, model diagnostics and residual plots	

11.11. Appendix 11: Example Mock Shells for Data Displays

Example : EFF_F1
Protocol : OTX116505
Population : Safety

Figure X.XX

Model Adjusted Mean (95% CI) Change from Baseline Plot: C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test

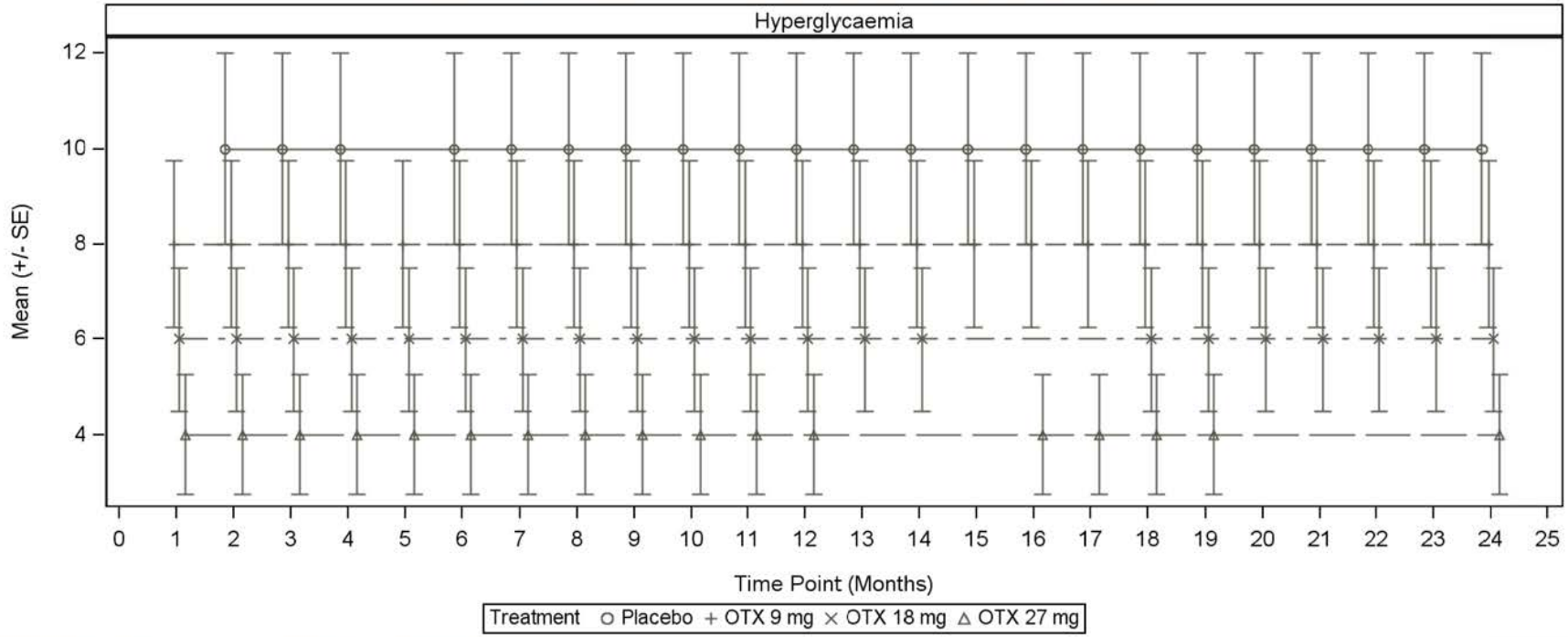


Programming Notes :	[1] Include C-Peptide and Glucose. [2] Use OTX instead of OTE for treatment labels.

[3] An OTX 36 mg will not be included in the data (not dosed)

Example : EFF_F2
Protocol : OTX116505
Population : Safety

Figure X.XX
Mean (+/- SE) Number of hyperglycemic and hypoglycemic events by month



Programming Notes : [1] Example only; actual event rates are not assumed to stay constant over month.

Example : EFF_F3
Protocol : OTX116505
Population : Safety

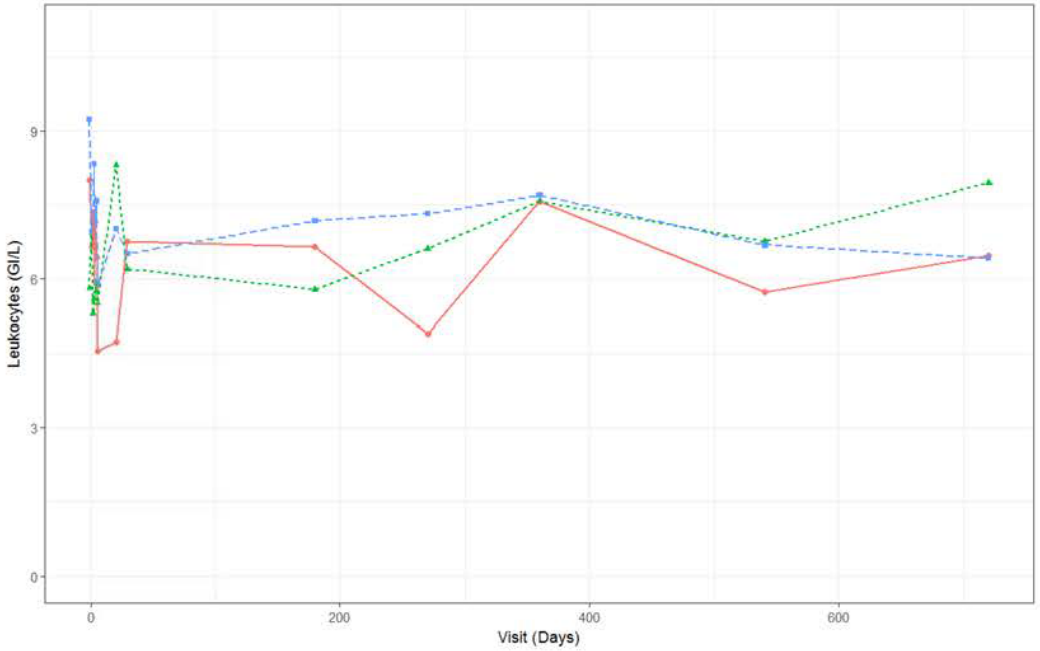
Figure X.XX
Mean (+/- SE) Change from Baseline in Frequency and phenotype of lymphocyte subsets by flow cytometry by C-Peptide Response

Programming Notes :	Similar to EFF_F1, but with: [1] Line by C-Peptide Responder Status [2] Panel by treatment

Example : SAF_F1
Protocol : OTX116505
Population : Safety

Figure X.XX
Individual Subject Plot - Hematology & Clinical Chemistry Selected Parameters

Category: Hematology; Parameter: Leukocytes (GI/L)
Treatment: Placebo; Time Span: All data



PPD

Programming Notes :	Similar to EFF_F1, but with:

[1] Line by C-Peptide Responder Status
[2] Panel by treatment

Example : SAFE_T1

Table SAFE_T1 has been deprecated and will not be used.

Example : **SAFE_T2**
Protocol : OTX116505
Population : Safety

Table X.XX
Summary (Absolute and Change from Baseline) of Epstein-Barr Virus (Viral Load: PCR)

Summary: Absolute

Treatment	Time	N	n	Mean/Geo. Mean	95% Confidence Interval for Geometric Mean	CVb%	Min	Median	Max
Placebo	X	x	x	xxx.x/xxx.x	xxx.x; xxx.x	XX%	xxx	xxx	Xxx
	X	x	x	xxx.x/xxx.x	xxx.x; xxx.x	XX%	xxx	xxx	Xxx
	X	x	x	xxx.x/xxx.x	xxx.x; xxx.x	XX%	xxx	xxx	Xxx
	.	.		.	. .		.	.	.
OTX 9 mg	X	x	x	xxx.x/xxx.x	xxx.x; xxx.x	XX%	xxx	xxx	Xxx
	X	x	x	xxx.x/xxx.x	xxx.x; xxx.x	XX%	xxx	xxx	Xxx
	X	x	x	xxx.x/xxx.x	xxx.x; xxx.x	XX%	xxx	xxx	Xxx
	.	.		.	. .		.	.	.
	.	.		.	. .	.	.	.	.

Continue for other doses

Programming Notes :	[1] For applicable endpoints, include parameter as either a BY parameter or as first column in the table [2] CVb%: calculate SD on log scale and then CVb% = 100*sqrt(exp(SD^2)-1)) with SD being the SD on log scale.

Example : **SAFE_T2 (Continued)** Page 1 of X
Protocol : OTX116505
Population : Safety

Table X.XX
Summary (Absolute and Change from Baseline) of Epstein-Barr Virus (Viral Load: PCR)

Summary: Change from Baseline

ETC

Programming Notes :	[1] For applicable endpoints, include parameter as either a BY parameter or as first column in the table

Example : SAFE_T3
Protocol : OTX116505
Population : Safety

Table X.XX
Summary of Categorical values of Epstein-Barr Virus (Serology:IgG & IgM)

					Number of Subjects (%)					
					Absolute Values		Change from Baseline			
Parameter	Visit	Treatment	N	n	Positive	Negative	Positive-Positive	Positive-Negative	Negative-Positive	Negative-Negative
Epstein-Barr IgG Antibody	Screening	Placebo	XX	XX	XX (%)	XX (%)				
		OTX 9 mg	XX	XX	XX (%)	XX (%)				
		OTX 18 mg	XX	XX	XX (%)	XX (%)				
		OTX 27 mg	XX	XX	XX (%)	XX (%)				
	Day -1	Placebo	XX	XX	XX (%)	XX (%)				
		OTX 9 mg	XX	XX	XX (%)	XX (%)				
		OTX 18 mg	XX	XX	XX (%)	XX (%)				
		OTX 27 mg	XX	XX	XX (%)	XX (%)				
	.									
	Day 6	Placebo	XX	XX	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)
		OTX 9 mg	XX	XX	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)
		OTX 18 mg	XX	XX	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)
		OTX 27 mg	XX	XX	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)	XX (%)

Example : **SAFE_T4**
Protocol : OTX116505
Population : Safety

Table X.XX
Categorical Summary of Epstein-Barr Virus (Viral Load: PCR)

Unit: copies/10^6PBM cells

Treatment	Visit	N	n	Number of Subjects (%) 0-1000	>1000-10000	>10000-100000	>100000
Placebo	X	x		XX (%)	XX (%)	XX (%)	XX (%)
	X	x		XX (%)	XX (%)	XX (%)	XX (%)
	X	x		XX (%)	XX (%)	XX (%)	XX (%)
	.	.					
OTX 9 mg	X	x		XX (%)	XX (%)	XX (%)	XX (%)
	X	x		XX (%)	XX (%)	XX (%)	XX (%)
	X	x		XX (%)	XX (%)	XX (%)	XX (%)
	.	.		.	.	.	.
	.	.		.	.	.	.

ETC

Programming Notes : [1] For applicable endpoints, include parameter as either a BY parameter or as first column in the table

Example : **EFF_T1**
Protocol : OTX116505
Population : Safety

Table X.XX

Summary Statistics (Absolute and Change from Baseline): C-Peptide & Glucose from Mixed Meal Tolerance Test

Parameter: C-peptide Weighted Mean AUC 0-120 mins (nmol/L)

Treatment	N	Visit	Variable	n	Mean	95% Confidence Interval	SD	Min	Median	Max
Placebo	X	Screening	Abs.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		Month 3	Abs.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		XXXX	Chg.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		Month 6	Abs.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		XXXX	Chg.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		XXXX		X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
OTX 9 mg		XXXX		X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		XXXX		X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		XXXX		X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
.					.	. .	.	.	.	.

ETC

Programming Notes : [1] For applicable endpoints, include parameter as either a BY parameter or as first column in the table

Example : **EFF_T1 (Continued)** Page 1 of X
Protocol : OTX116505
Population : Safety

Table X.XX

Summary Statistics (Absolute and Change from Baseline): C-Peptide & Glucose from Mixed Meal Tolerance Test

Summary: Change from Baseline

Please use same shell as for absolute values

Programming Notes :	[1] For applicable endpoints, include parameter as either a BY parameter or as first column in the table [2] If later it is decided to use log-transformation instead, then please use SAFE T-2 as template for them. [3]: If not all columns fit on one page, please switch to PD_T1 instead.

Example : **EFF_T2**
Protocol : OTX116505
Population : Safety

Table X.XX

Summary of Statistical Analysis (MMRM) Results of Change from Baseline: C-Peptide & Glucose Weighted Mean AUC(0-120 mins) from Mixed Meal Tolerance Test

Parameter:

Visit	Statistic	Placebo N=xx	OTX 9 mg N=xx	OTX 18 mg N=xx	OTX 27 mg N=xx
Month 3	n(1)	xx	xx	xx	xx
	n(2)	xx	xx	xx	xx
	LS Mean	x.xx	x.xx	x.xx	x.xx
	LS Mean Change	x.xx	x.xx	x.xx	x.xx
	Standard Error	x.xxx	x.xxx	x.xxx	x.xxx
	Difference from Placebo		x.xx	x.xx	x.xx
	95% Confidence Interval		x.xx - x.xx	x.xx - x.xx	x.xx - x.xx
	P-value		0.xxx	0.xxx	0.xxx

Footnotes :	n(1) = Number of subjects in analysis; n(2) = Number of subjects with data at that visit P-value tests the null hypothesis of no difference from placebo.
Programming Notes	Use three decimal places for p-values. Always use ceiling instead of rounding (i.e. show 0.0501 as 0.051 and not 0.050. If the p-value is smaller than 0.001 display as "< 0.001".

Example : EFF_T3
Protocol : OTX116505
Population : Safety

Table X.XX
Summary of Hypoglycaemic & Hyperglycaemic Events and Event Rates

Hypoglycaemic Events

Time Period Category	Placebo (N=xxx) n (%)	Placebo (N=xxx) Number of Events / Mean [1]	Placebo (N=xxx) Time Normalized Number of Events / Mean [2]	9mg (N=xxx) n/N (%)	9mg (N=xxx) Number of Events / Mean [1]	9mg (N=xxx) Time Normalized Number of Events / Mean [2]
Any Time Post-dose						
Number of Subjects	X			X		
Any Hypoglycemia	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx/xxx (xx%)	xxx / xx.x	xxx / xx.x
Hypoglycemia Grade 1	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx/xxx (xx%)	xxx / xx.x	xxx / xx.x
Hypoglycemia Grade 2	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx/xxx (xx%)	xxx / xx.x	xxx / xx.x
Hypoglycemia Grade 3	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx/xxx (xx%)	xxx / xx.x	xxx / xx.x
…						
Dosing Period						
Number of Subjects	X			X		
Any Hypoglycemia	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx (xx%)	xxx / xx.x	xxx / xx.x
Hypoglycemia Grade 1	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx (xx%)	xxx / xx.x	xxx / xx.x
Hypoglycemia Grade 2	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx (xx%)	xxx / xx.x	xxx / xx.x
Hypoglycemia Grade 3	xxx (xx%)	xxx / xx.x	xxx / xx.x	xxx (xx%)	xxx / xx.x	xxx / xx.x
..						

[1] Number of Events = the total number of events at each level of summarization. Mean = the average

number of events reported per subject.

[2] Normalized by dividing Number of Events by length of reporting period in month (1 month = 30 days). Mean = the average event rate reported by subject. Subjects are only included if they had both visits delimiting the reporting period.

Programming Notes :	[1] Please show same categories as AE tables by grade: grades 1,2,3,4,5 as well as grade 3+4+5 and unknown (if any). [2] Continue with Post-dose up to Week 6 Visit, Post Week 6 Visit to Month 3 Visit, Post Month 3 Visit to Month 6 visit then similarly, 6-9, 9-12, 12-18, 18-24. Please continue with Hyperglycaemic events and update the footnote accordingly. Please use the Number of Subjects row in each column as the denominator for the percentages, not the overall N.

Example : EFF_T4
Protocol : OTX116505
Population : Safety

Table X.XX
Number and Percent of Subjects Meeting Definition of Glycemic Responder

	Visit	Responder Status	Placebo N =XX	OTX 9 mg	OTX 18 mg	OTX 27 mg
Glycemic Response	Week 4	Responders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
		Non-responders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
		New responders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
		Non-responders who were responders at previous visit	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Week X	...				

Note: a subject is a glycemic responder, if he fulfils the following criteria:
1. HbA1c <= 7%
2. Mean daily insulin use < 0.5 units/kg/day.

Example : **EFF_T5**
Protocol : OTX116505
Population : Safety

Table X.XX

Summary Statistics (Absolute and Change from Baseline): Frequency and phenotype of lymphocyte subsets by flow cytometry by C-Peptide Response

Parameter: XXXXX (UNIT)

Summary: Absolute

		Placebo N=XX		OTX 9 mg N=XX		OTX 18 mg N=XX		OTX 27 mg N=XX	
Visit	Statistic	Non-responders	Responders	Non-responders	Responders	Non-responders	Responders	Non-responders	Responders
Screening	n	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	95% Confidence Interval	xxx.x; xxx.x	xxx.x; xxx.x	xxx.x; xxx.x	xxx.x; xxx.x	xxx.x; xxx.x	xxx.x; xxx.x	xxx.x; xxx.x	xxx.x; xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Max	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
…	…	.							

ETC

Programming Notes :	Footnotes: [1] A participant is considered a C-peptide responder if there is >-40% change from baseline in C-peptide MMTT Weighted Mean AUC (0-120) after 24 months.

[2] Subjects with missing responder status due to missing C-peptide at 24 months are not included in the table.

Example : PD_T1
Protocol : OTX116505
Population : Safety

Table X.XX
Summary Statistics (Absolute and Change from Baseline): Target Engagement

Parameter: XXXXX

Treatment	N	Visit, Time	Variable	n	Mean	95% Confidence Interval	SD	Min	Median	Max
Placebo	X	Day 1, 00:00	Abs.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
			Chg.	X	xxx.x	xxx.x, xxx.x	xx.xx	xxx	xxx	Xxx
		...								
OTX 9 mg										
.					.	.	.	.	.	.	.
ETC										

Example : OTHER_L1

Protocol : OTX116505
Population : Safety

Listing XX
Listing of C-Peptide & Glucose from Mixed Meal Tolerance Test

Treatment:Placebo

Inv./ Subj.	Age(yrs)/ Sex/ Race	Visit	Date/ Study Day	Planned/Actual Relative Time (Mins)	Time Sample Taken	C-Peptide (Units)	Glucose (Units)
XXXXX/ XXX	XX/ Male/ White	XXXX	DDMMMYYYY / XX	X / X	HH:MM	XXX.XX	XXX.XX
				X	HH:MM	XXX.XX	XXX.XX
				X	HH:MM	XXX.XX	XXX.XX
				X	HH:MM	XXX.XX	XXX.XX
				X	HH:MM	XXX.XX	XXX.XX
		XXXX	DDMMMYYYY	X	HH:MM	XXX.XX	XXX.XX
				X	HH:MM	XXX.XX	XXX.XX
				X	HH:MM	XXX.XX	XXX.XX

Programming Notes : [1] As required to be modified based on data and any applicable IDSL standard principles for listings

Example : OTHER_L2

Protocol : OTX116505
Population : Safety

Listing XX

Listing of C-Peptide & Glucose from Mixed Meal Test: Derived Parameters

Treatment: Placebo

Inv./Subj.	Age(yrs)/ Sex/ Race	Analyte	Visit	Date/Study Day	Time Int. For Derivation (Mins)	Weighted Mean AUC(0-120M) Results	Change from Baseline Weighted Mean AUC(0-120M)
XXXXX/ XXX	XX/ Male/ White	XXXXX	XXXX	DDMMMYYYY / XX	XXX	X.XXX	X.XXX
			XXXX		XXX	X.XXX	X.XXX
			XXXX		XXX	X.XXX	X.XXX
			XXXX		XXX	X.XXX	X.XXX
		XXXXX	XXXX			X.XXX	X.XXX
			XXXX			X.XXX	X.XXX
			XXXX			X.XXX	X.XXX
			XXXX			X.XXX	X.XXX

Programming Notes : [1] As required to be modified based on data and any applicable IDSL standard principles for listings

Example : OTHER_L3
Protocol : OTX116505
Population : Safety

Listing XX
Listing of Immunogenicity Results

Treatment: Placebo

Inv./ Subj.	Age(yrs)/ Sex/ Race	Visit	Date/Time sample Taken	Screening Result	Confirmation Result	Titer
Xxxx/ xxx	XX/ Male/ White	Day -1	DDMMMYYYY/Hh:mm	Positive	Positive	X

Programming Notes :	[1] As required to be modified based on data and any applicable IDSL standard principles for listings

Example : OTHER_L4
Protocol : OTX116505
Population : Safety

Listing XX
Listing of Auto-Antibody Results

Treatment:Placebo

Inv./ Subj.	Age(yrs)/ Sex/ Race	Visit	Date	Study Day	Time	Result	Unified Classification
Xxxx/ xxx	27/ Male/ White	Screening	DDMMMYYYY	XX	XX:XX	XXXX	XXXX

Programming Notes : [1] As required to be modified based on data and any applicable IDSL standard principles for listings

Example : OTHER_L5
Protocol : OTX116505
Population : Safety

Listing XX
Listing of Hypoglycemic & Hyperglycemic Event Rates

Treatment: Placebo

Inv./ Subj.	Age(yrs)/ Sex/ Race	Event Type	Reporting Period	Number of Events	Start/End Date of Reporting Period	Duration of reporting period (months)	Event Rate (1/month)
Xxxx/ xxx	27/ Male/ White	Hypoglycemic	Overall (up to 24 months visit)	XXXX	DDMMMYYYY/ DDMMMYYYY	XXX	XXXX
			Post-dose Dosing Period	XXXX	DDMMMYYYY/ DDMMMYYYY	XXXX	XXXX
			Post Dosing Period up to 6 weeks	XXXX	DDMMMYYYY/ DDMMMYYYY	XXXX	XXXX
			6 weeks to 3 months	XXXX	DDMMMYYYY/		

Footnotes:	For the purpose of this listing one month is assumed to have 30 days. Duration of period and event rate will only be calculated if the visit at the end of the reporting period took place.
Programming Notes :	[1] As required to be modified based on data and any applicable IDSL standard principles for listings

Example : OTHER_L6
Protocol : OTX116505
Population : Safety

Listing XX
Listing of Insulin Use

Treatment: Placebo

Inv./ Subj.	Age(yrs)/ Sex/ Race	Study Day	Date/Time	Reported Name/ Standardized Name	Dose	Unit	Last Recorded Weight Prior to Intake (kg)	Standardized Dose (IU/kg)
Xxxx/ xxx	27/ Male/ White	XXXX	DDMMMYYYY/Hh:mm	XXXXX/XXXXX				
		XXXX	DDMMMYYYY/Hh:mm					
		XXXX	DDMMMYYYY/Hh:mm					
		XXXX	DDMMMYYYY/Hh:mm					
		Day -1 Mean Use						

Footnotes:	For the purpose of this listing one month is assumed to have 30 days. Duration of period and event rate will only be calculated if the visit at the end of the reporting period took place.
Programming Notes :	[1] As required to be modified based on data and any applicable IDSL standard principles for listings [2] If all units are IU or convertible to IU combine Dose and Unit columns to a single Column Dose (IU)

Example: OTHER_L7
Protocol : OTX116505
Population : Safety

Listing XX
Cardiovascular Events

Treatment	Inv./ Subj.	Age(yrs)/ Sex/ Race	Visit	Date	Cardiovascular Events	Events
xxxx	XXXXX/ XXXXX	27/ Male/ White	XXX	DDMMMYYYY	No	
					Yes	Congestive Heart Failure
						Pulmonary Hypertension
					No	

Example : OTHER_L8
Protocol : OTX116505
Population : Safety

Listing XX
Listing of C-Peptide & Glucose from Clamp

Treatment:Placebo

Inv./ Subj.	Age(yrs)/ Sex/ Race	Visit	Date/ Study Day	Phase	Planned/Actual Relative Time (Mins)	Time Sample Taken	Glucose Infusion Concentration and Rate (ml/hr).	C-Peptide (Units)	Glucose (Units)
XXXXX/ XXX	XX/ Male/ White	XXXX	DDMMMYYYY / XX	Euglycemic	X / X	HH:MM	Gluc 10%, 50ml/hr	XXX.XX	XXX.XX
					X	HH:MM	Gluc 20%, 100 ml/hr	XXX.XX	XXX.XX
				Hyperglycemic	X	HH:MM	NaCl, 50 ml/hr	XXX.XX	XXX.XX
					X	HH:MM	…	XXX.XX	XXX.XX
					X	HH:MM		XXX.XX	XXX.XX
		XXXX	DDMMMYYYY/XX		X	HH:MM		XXX.XX	XXX.XX
					X	HH:MM		XXX.XX	XXX.XX
					X	HH:MM		XXX.XX	XXX.XX

Programming Notes : [1] As required to be modified based on data and any applicable IDSL standard principles for listings

Example : OTHER_L9

Protocol : OTX116505
Population : Safety

Listing XX

Listing of C-Peptide & Glucose from Clamp: Derived Parameters

Treatment: Placebo

Inv./ Subj.	Parameter	Visit	Date/Study Day	Time Int. For Derivation (Mins)	Result	Change from Baseline
XXXXX/ XXX	Glucose Weighted Mean AUC(60-140M) (UNIT)	XXXX	DDMMMYYYY / XX	XXX	X.XXX	X.XXX
		XXXX		XXX	X.XXX	X.XXX
		XXXX		XXX	X.XXX	X.XXX
		XXXX		XXX	X.XXX	X.XXX
	xxxx	XXXX			X.XXX	X.XXX
		XXXX			X.XXX	X.XXX
		XXXX			X.XXX	X.XXX
		XXXX			X.XXX	X.XXX

Programming Notes :	[1] As required to be modified based on data and any applicable IDSL standard principles for listings [2] Include the following parameters: Glucose weighted mean (60-140), C-Peptide weighted mean (60-140), Insulin Sensitivity

Example : OTHER_L10
Protocol : OTX116505
Population : Safety

Listing XX
Listing of Family History of Cardiovascular Risk

Treatment: Placebo

Inv./ Subj.	Family History Classification	Family History Relative	Family History of Premature Coronary Disease
XXXXX/ XXX	Cardiovascular Risk Factor	First Degree Relative	

Footnote	Premature is defined when occurring before 65 years in women or before 55 years in men. Only first degree relatives are considered.

Example : OTHER_L11
Protocol : OTX116505
Population : Safety

Listing XX
Listing of Substance Use

Treatment: Placebo

Inv./ Subj.	History of Smoking Status	Date of Last Smoking	Alcohol Consumption	Average Number of Units
XXXXX/ XXX	Former smoker	DDMMMYYYY		

Footnote	Premature is defined when occurring before 65 years in women or before 55 years in men. Only first degree relatives are considered.

Example : OTHER_L12

Protocol : OTX116505
Population : Safety

Listing XX

Listing of Epstein-Barr Virus Serology: IgG & IgM and Viral Load Treatment: Placebo

Inv./Subj.	Age(yrs)/ Sex/ Race	Visit	Date/Study Day	Test (Unit)	Result	Change from Baseline
XXXXX/ XXX	XX/ Male/ White	XXXX	DDMMMYYYY / XX			
		XXXX				
		XXXX				
		XXXX				
		XXXX				
		XXXX				
		XXXX				
		XXXX				

Programming Notes : [1] As required to be modified based on data and any applicable IDSL standard principles for listings

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