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

Title	:	Reporting and Analysis Plan for Study GLP110933: Albiglutide versus Placebo in insulin-treated Subjects with new-onset type 1 diabetes mellitus
Compound Number	:	GSK716155
Effective Date	:	01-DEC-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) and study disclosure related reporting for Protocol GLP110933.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP details all planned analyses and outputs required for the final Clinical Study Report (CSR) and study disclosure related reporting of study GLP110933.
Protocol	• This RAP is based on the amended protocol (Dated: 12/SEP/2014) of study GLP110933 (GlaxoSmithKline Document Number.: 2011N125236_02 and eCRF Version 11.0).
Primary Objective	• Determine the effect of albiglutide therapy versus placebo on endogenous insulin secretion over 52 weeks when added to standard of care (background insulin therapy) in subjects with New Onset Type I Diabetes Mellitus (NOT1DM).
Primary Endpoint	• Mean change from baseline in stimulated (from mixed meal tolerance test [MMTT]) 2 hour plasma C-peptide area under the curve (AUC) at Week 52
Study Design	• This is a Phase II, randomised, double-blind, parallel group, placebo-controlled, multicentre study of 52 weeks treatment duration in subjects with NOT1DM. • Approximately 68 eligible subjects will be randomised in a 3:1 ratio such that 51 subjects receive albiglutide 30 mg once weekly (with blinded increase to 50 mg once weekly at Week 6 if the 30 mg dose is tolerated) added-on to insulin therapy and 17 subjects receive placebo once weekly added-on to insulin therapy. Historical data from placebo patients, aged 18-30 from the DEFEND-1 study [GlaxoSmithKline Document Number, 2011N125757_00] will be incorporated into the primary endpoint analysis, using Bayesian analysis. • Blinded reduction of randomised study medication to the 30 mg once weekly dose may occur in the event of GI intolerability (i.e., nausea, vomiting or diarrhoea) after discussion between the investigator and medical monitor. • During the study, subjects will perform self-monitored plasma glucose monitoring at least 4 times daily and adjust their basal and meal-time insulin requirements according to protocol-defined algorithm/guidance. • A sample size of 60 evaluable subjects (45 in the albiglutide group and 15 in the placebo group) provides 90% power to detect a treatment effect in the primary endpoint of the current study in the range of 0.19 nmol/L (using data from all 53 placebo subjects aged 18-30 from the DEFEND-1 study) to 0.30 nmol/L (not using any historical data). The corresponding minimal detectable difference will be 0.12 nmol/L to 0.18 nmol/L, respectively. • The total duration of a subject's participation will be approximately 72 weeks (up to 8 weeks of Screening, 52 weeks of treatment and 12 weeks of Post-treatment Follow-up).
Planned Analyses	• No interim analysis is planned for this study. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to unblinding of the study data.

Overview	Key Elements of the RAP
Analysis Populations	• The 'Intent to Treat' Population will be used to evaluate study efficacy. The 'Safety' Population will be used to evaluate study population characteristics, safety and PD/Biomarkers, and the 'PK' Population to evaluate pharmacokinetics.

Hypothesis	• The primary endpoint analysis, incorporating historical placebo data from the DEFEND-1 study, will be performed using a Bayesian analysis and will therefore not utilise hypothesis testing.
	• Sensitivity analyses for the primary Bayesian analysis will be performed, using 0% historical placebo data and 100% historical placebo data.
	• In addition, a non-Bayesian sensitivity analysis of the primary endpoint (excluding historical placebo data from the DEFEND-1 study) will test the following hypothesis:
	  • The primary efficacy analysis endpoint will be Change from Baseline in stimulated 2 hour MMTT C-peptide AUC at Week 52 following one year of treatment. Letting λ be the difference of 2-hr MMTT C-peptide AUC at week 52 between albiglutide and placebo, then
	  • Null hypothesis: $\lambda = 0$
	  • Alternative hypothesis: $\lambda \neq 0$

Primary Analyses	• The primary analysis of change from baseline in 2 hour MMTT plasma C-peptide AUC at Week 52 will be performed using a Bayesian analysis incorporating historical placebo data from the DEFEND-1 study using a robust mixture prior (with w=0.5). • Sensitivity analyses will be performed.
Secondary Analyses	• Efficacy endpoints will be separately analysed using suitable mixed models repeated measures analyses. Point estimates, corresponding 95% confidence intervals and p-values (2-sided, 5% level) will be constructed for the adjusted differences between albiglutide and placebo. • Change from baseline in continuous endpoints will be analysed using a MMRM model with appropriate baseline covariates. Response endpoints will be analysed using a non-parametric, covariance-adjusted, extended Mantel-Haenszel test. • Safety data will be presented in tabular format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. • Exploratory endpoints will not be summarised. Data will be listed only.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• The protocol specified that for the primary efficacy analysis 'Historical placebo information with 50% weight will be incorporated into the mixed effect model by Bayesian modelling using SAS PROC MCMC procedure'. • Also, 'The above repeated mixed-effects model analysis will be repeated without placebo information from DEFEND-1, and with 100% placebo information from the DEFEND-1 study as sensitivity analyses'	• The primary efficacy analysis using 50% weight for historical information has been replaced by a Bayesian analysis which incorporates historical placebo data from the DEFEND-1 study using a robust mixture prior. The weighting for the robust mixture prior will be w=0.5. • The sensitivity analyses without placebo data from DEFEND-1 and using 100% placebo data from DEFEND-1 will be performed using w=0 and w=1 respectively.	• This methodology allows the weighting of historical DEFEND-1 placebo data to depend on the similarity to the albiglutide GLP110933 study data. • It has been recommended as an improved approach by experts on Bayesian analysis within GSK.
• The protocol describes the primary Bayesian analysis as a mixed-effects model.	• The RAP has removed the terminology 'mixed-effects' from the description of the Bayesian analysis.	• The Bayesian approach is to treat all parameters as random. This change was recommended as an improved description of the Bayesian analysis.
• The protocol specified the primary Bayesian analysis model included the main effects of treatment group and visit, in addition to the treatment group-by-visit interaction term.	• The main effects of treatment group and visit have been removed from the model for the primary Bayesian analysis. • The main effect terms remain in non-Bayesian models.	• Including the main effects in addition to the interaction term has a potential impact on likelihood of convergence. • The non-Bayesian models keep these terms (as specified in the protocol), as the treatment group-by-visit parameter estimates are not affected by their inclusion/removal.
• The protocol specified that sensitivity analyses for the primary analysis would be performed including:	• These sensitivity analyses will not be performed, however they may be done as post-hoc sensitivity	• Given the small number of subjects in the study it is felt that statistical analyses should be kept to a

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• A test for treatment group-by-time (continuous) interaction • Examining the C-peptide AUC data for a trend over time.	analyses if needed.	minimum. If study results indicate these analyses would be useful then they may be performed as post-hoc sensitivity analyses.
• The protocol specifies that the secondary efficacy endpoints will be analysed at all time-points that they are recorded at.	• Secondary efficacy variables will have statistical analyses performed at Week 28 and Week 52 only. These endpoints include maximum stimulated C-peptide, plasma glucagon, responders, partial remission status, HbA1c, mean daily insulin and weight. • Only C-peptide AUC will have statistical analyses performed at other time-points (i.e., weeks 16, 28, 52 and 64).	• The company is not developing Albiglutide for Type 1 diabetes mellitus so statistical analysis of secondary endpoints will be limited to Week 28 and 52 only. • Other time-points will be summarised using descriptive statistics only.
• Exploratory endpoints will be descriptively summarised, graphically presented and listed.	• Exploratory endpoints will not be summarised or presented graphically. Data will be listed only.	• The company is not developing Albiglutide for Type 1 diabetes mellitus so exploratory endpoints will be listed only.
• The protocol objectives described a responder as 'having HbA1c $\leq$7.0% and mean daily insulin use < 0.5 units/kg/day'; the endpoint section described responders as 'HbA1c <7.0% and insulin dose < 0.5 units/kg/day'.	• Responders are defined as 'having HbA1c $\leq$7.0%' and mean daily insulin use/insulin dose <0.5 units/kg/day.	• To clarify the inconsistency in the protocol for the definition of responders (i.e., HbA1c $\leq$ or < 7.0%).
• The protocol specified 'the mean daily insulin use value will be calculated in units/kg/day, as the mean of the values of the total amount of insulin used per day on each of the 3 consecutive days'	• The mean daily use value will be calculated as the sum of the average prandial insulin doses and the average basal insulin doses for each subject over the 3 consecutive days	• To better represent the mean daily insulin value given the data collection issues for this endpoint.
• The protocol defined a secondary endpoint 'Change from Baseline in body weight (kg) at Week 52 and Weight over time (i.e., at Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64)'; but the statistical section did not contain	• Change from baseline in body weight will be summarised over time, and will be analysed statistically at Week 28 and Week 52, using a MMRM analysis similar to the primary	• To clarify the analysis and reporting of this secondary endpoint. • No changes to the endpoint wording.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
any details on the summary or analysis of this endpoint.	endpoint.	
• The protocol defined a secondary objective of 'Determine any differences in significant hypoglycaemia (i.e., events with plasma glucose <3.9 mmol/L and/or requiring third party intervention) between treatment groups' • Related endpoint of 'Number of events of hypoglycaemia with confirmed self plasma glucose monitoring <3.9 mmol/L and/or requiring third party intervention (i.e., severe, documented symptomatic and asymptomatic hypoglycaemic events) occurring > Week 24 and ≤Week 52	• 'Determine any differences in significant hypoglycaemia (i.e., events with plasma glucose ≤3.9 mmol/L and/or requiring third party intervention) between treatment groups' • 'Number of events of hypoglycaemia with confirmed self plasma glucose monitoring ≤3.9 mmol/L and/or requiring third party intervention (i.e., severe, documented symptomatic and asymptomatic hypoglycaemic events) occurring > Week 24 and ≤Week 52	• The ADA classification of documented symptomatic and asymptomatic hypoglycaemic events requires a plasma glucose ≤3.9 mmol/L. In order to make the objective and endpoint consistent with the ADA classification the glucose level has been changed from '<3.9 mmol/L' to '≤3.9 mmol/L' • Other endpoints which reference <3.9 mmol/L have also been changed to ≤3.9 mmol/L, for consistency (i.e. 7-point glucose profile and 72h CGM).
• 7 point glucose profile: The protocol defined a secondary endpoint 'Number and magnitude of hypoglycaemic (<3.9 mmol/L) and hyperglycaemic excursions (>10.0 mmol/L) from the 7 point glucose profile at Baseline, Week 28 and Week 52' • 72-hour CGM: The protocol defined a secondary endpoint as 'Time spent with a plasma glucose <3.9 mmol/L, between 3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52'	• 'Number and magnitude of hypoglycaemic (≤3.9 mmol/L) and hyperglycaemic excursions (>10.0 mmol/L) from the 7 point glucose profile at Baseline, Week 28 and Week 52' • 'Time spent with a plasma glucose ≤3.9 mmol/L, between >3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52'	• As described above, the definition of hypoglycaemia has been changed from <3.9 mmol/L to ≤3.9 mmol/L for consistency with the ADA classification.
• 72-hour CGM: The protocol defined a secondary endpoint as 'Time spent with a plasma glucose <3.9 mmol/L, between 3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52; but the statistical section did not contain any details on the	• Change from baseline in time spent with plasma glucose ≤ 3.9 mmol/L; with plasma glucose between >3.9 mmol/L and 10.0 mmol/L; and with plasma glucose >10.0 mmol/L at Week 28 and Week 52 • Statistical analysis will be performed separately for	• To clarify that statistical analysis would be performed for this endpoint, and to describe the statistical analysis.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
statistical analysis of this endpoint.	the 3 endpoints using MMRM methods. • Results should be interpreted with caution due to correlation between endpoints.	
• 'In analyses of HbA1c and insulin usage, missing data at key analysis time points will be imputed using the last observation carried forward method.'	• The imputation of missing data using the last observation carried forward method will not be done for HbA1c or insulin usage. • No imputation of missing data. The MMRM methodology will be used for statistical analysis.	• Feedback from the FDA for a different albiglutide study indicated that the LOCF approach was no longer acceptable.
• The protocol states 'Laboratory values below the level of quantification (BLQ) will be set to one-half the limit of quantification (unless noted otherwise) in computations for the aggregate analyses, but will be noted as BLQ in the listings'	• Laboratory results that are beyond the limits of quantification will have the inequality sign dropped (<, ≤, >, or ≥) and the quantification limit will be used as the numeric result for summarisation.	• To be consistent with how these values are handled in other albiglutide studies.
• The protocol specified that 'age group' would fitted as an independent variable in the mixed effects model	• Age (years) will be fitted as a continuous covariate where the statistical models allow.	• To better allow for the effect of age which could not be easily categorised into meaningful groups
• In the mixed effect model specification baseline-by-visit interaction was not included as a term in the model.	• 'Inclusion of the term baseline-by-visit may be considered in the final model based on model fit and/or convergence.'	• In order to allow differences in treatment response according to baseline value; however due to the small sample size in this study there may be convergence problems when including this additional term.
• The protocol specifies 'a test for treatment group-by-time (continuous) interaction in the model (adjusted for baseline value and randomisation strata)'	• 'a test for treatment group-by-time (continuous) interaction in the model (adjusted for baseline value and age)'	• To correct the protocol text, as the randomisation is not stratified in this study. The correct covariate should have been age.
• The protocol specified 'If a laboratory test is repeated because of an apparent error, the repeat test result will be used in place of the original test result. Both the original test result and the repeat test result will be shown in the listings'	• This sentence has been deleted. • Laboratory data will be summarised by nominal visit, unscheduled values will be included in summaries of worst-case results at any time post	• To clarify how programming will handle these laboratory assessments, as repeat laboratory tests will not be included in by-visit summaries.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	baseline (e.g. results of potential clinical interest, out of normal range).	
• Secondary endpoint: Population estimates of PD parameters (e.g., Emax, EC_{50}), associated inter-subject variability and residual error if permitted by the data	• Analysis of this endpoint will not be conducted.	• The company is not developing Albiglutide for Type 1 diabetes mellitus so analysis of this endpoint will not be conducted.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Determine the effect of albiglutide therapy versus placebo on endogenous insulin secretion over 52 weeks when added to standard of care in subjects with new onset type 1 diabetes mellitus (NOT1DM)	• <u>Primary Endpoint:</u> Mean change from baseline in stimulated (from mixed meal tolerance test [MMTT]) 2 hour plasma C-peptide area under the curve (AUC) at Week 52 • <u>Secondary Endpoints linked to primary objective:</u> Mean change from baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 16, 28 and Week 64 Maximum stimulated plasma C-peptide: the highest value at any time point during the 2 hour MMTT after the subject has ingested the mixed meal at Baseline, Week 16, Week 28, Week 52 and Week 64
Secondary Objectives	**Secondary Endpoints**
• To assess the effect of albiglutide versus placebo on plasma glucagon concentration during a MMTT	• Mean change from baseline in plasma glucagon AUC (from MMTT) at Week 16, 28, 52 and Week 64
• Determine the percentage of subjects meeting the definition of a responder (defined as having HbA1c $\leq$ 7.0% and mean daily insulin use < 0.5 units/kg/day) and the percentage of subjects achieving partial remission status (i.e., defined as subjects with Insulin Dose Adjusted A1c (IDAA1C) $\leq$ 9.0)	• Percent of responders (defined as subjects with HbA1c $\leq$7.0% and insulin dose <0.5 units/kg/day) at Weeks 4, 8, 16, 28, 40, 52 and 64 • Percent of subjects achieving insulin dose-adjusted haemoglobin A1c (IDAA1C) $\leq$9.0 at Weeks 4, 8, 16, 28, 40, 52 and 64
• To assess glycaemic control in both treatment groups as measured by HbA1c	• Change from Baseline in HbA1c at Week 52 and HbA1c over time (i.e., at Weeks 4, 8, 16, 28, 40, 52 and 64)
• Determine differences in total daily insulin dose between treatment groups	• Change from baseline in mean daily insulin use over the 3 days preceding the visit at Weeks 4, 8, 16, 28, 40, 52 and 64. The mean daily insulin use value will be calculated, in units/kg/day, as the sum of average

Objectives	Endpoints
	prandial insulin doses and average of basal insulin doses for each subject recorded daily for the 3 days prior to the specified visits, divided by the subject's body weight in kg
• Determine any differences in significant hypoglycaemia (i.e., events with plasma glucose ≤3.9 mmol/L and/or requiring third party intervention) between treatment groups	• Number of events of hypoglycaemia with confirmed self plasma glucose monitoring ≤3.9 mmol/L and/or requiring third party intervention (i.e., severe, documented symptomatic and asymptomatic hypoglycaemic events) occurring >Week 24 and ≤Week 52
• Compare glycaemic variability between treatment groups, as measured by 72-hour continuous glucose monitoring (CGM) and 7 point glucose profile	• Time spent with a plasma glucose ≤3.9 mmol/L, between >3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52 • Number and magnitude of hypoglycaemic (≤3.9 mmol/L) and hyperglycaemic excursions (>10.0 mmol/L) from the 7 point glucose profile at Baseline, Week 28 and Week 52
• Determine the effect of albiglutide on body weight	• Change from Baseline in body weight (kg) at Week 52 and Weight over time (i.e., at Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64)
• Assess the safety and tolerability of albiglutide in subjects with NOT1DM	• Incidence of hypoglycaemia (in total and by each category as defined by ADA criteria) overall and in 3 monthly intervals (i.e., from Baseline to Week 12, >Week 12 to ≤Week 24, >Week 24 to ≤Week 36, >Week 36 to ≤Week 52, >Week 52 to ≤Week 64 • Incidence of hypoglycaemia with plasma glucose <3.1 mmol/L (< 56 mg/dL) regardless of symptoms • Incidence of daytime hypoglycaemia (in total and by ADA category) (defined as hypoglycaemic episodes with an onset between 06:00 h and 00:00 h (inclusive) and nocturnal hypoglycaemia (in total and by category) defined as hypoglycaemic episodes with an onset between 00:01 h and 05:59 h (inclusive) will be determined • Adverse events and serious adverse events • Other adverse events of special interest (AESI) (for example, cardiovascular, gastrointestinal, pancreatitis, malignancies (including pancreatic cancer and thyroid cancer), injection site reaction, liver events, potential systemic allergic reactions, atrial fibrillation/flutter, pneumonia, diabetic ketoacidosis [DKA i.e., ketonuria/ketonaemia, hyperglycaemia and acidaemia]) • Assessment of clinical laboratory tests (haematology, biochemistry, urinalysis)

Objectives	Endpoints
	• Assessment of vital signs measurements, 12-lead electrocardiograms (ECGs) and physical examinations • Immunogenicity (i.e., percentage of subjects developing anti-albiglutide antibodies and characterisation of anti-albiglutide antibodies)
• To evaluate the albiglutide PK profile in subjects with NOT1DM	• Population estimates of PK parameters (e.g., apparent clearance [CL/F], apparent volume of distribution [V/F], first-order absorption rate constant [K_a]), associated inter-subject variability and residual error • Covariates and covariate effects on subject PK • Population estimates of PD parameters (e.g., Emax, EC_{50}), associated inter-subject variability and residual error if permitted by the data
Exploratory Objectives	**Exploratory Endpoints**
• Assess the effect of albiglutide on T1DM-associated auto-antibodies (antibody to glutamic acid decarboxylase (anti-GAD) antibody to protein tyrosine phosphatase-like protein (anti-IA-2) and insulin autoantibody (IAA))	• Change from baseline in anti-GAD, anti-IA-2 and IAA antibody titres at Week 4, Week 16, Week 28, Week 40, Week 52 and Week 64
• Explore whether urinary C-peptide could be used in future phase III studies as an alternative to plasma C-peptide AUC from mixed meal testing as a measure of endogenous insulin secretion	• Correlation of urinary C-peptide 120 minute after a mixed meal (urinary creatinine corrected) with MMTT plasma C-peptide AUC assessed at Baseline, Week 16, Week 28, Week 52 and Week 64
• Evaluate the PK and PD (PK/PD) relationship between plasma albiglutide concentration and measures of glycaemic control (e.g., C-peptide, insulin use, HbA1c, etc) and other potential efficacy, tolerability (e.g., nausea and vomiting) and safety endpoints as data permit	• Graphical or model-based exploration of PK/PD relationships between albiglutide exposure (e.g., steady state AUC) and selected PD endpoints if appropriate and permitted by the data
• Assess the effect of albiglutide on biomarkers associated with autoimmune pathology over 52 weeks in subjects with NOT1DM	• A decision on whether to analyse biomarker samples will be made after review of efficacy endpoints at the end of the study. Exploratory biomarkers may include CD8-positive antigen-specific T-cells and biomarkers for β-cell death.
• Assess the effect of albiglutide on diabetes-related quality of life as measured by the Audit of Diabetes Dependent Quality of Life Questionnaire (ADDQoL).	• Change from baseline in ADDQoL global and domain scores and overview item scores at Week 52.

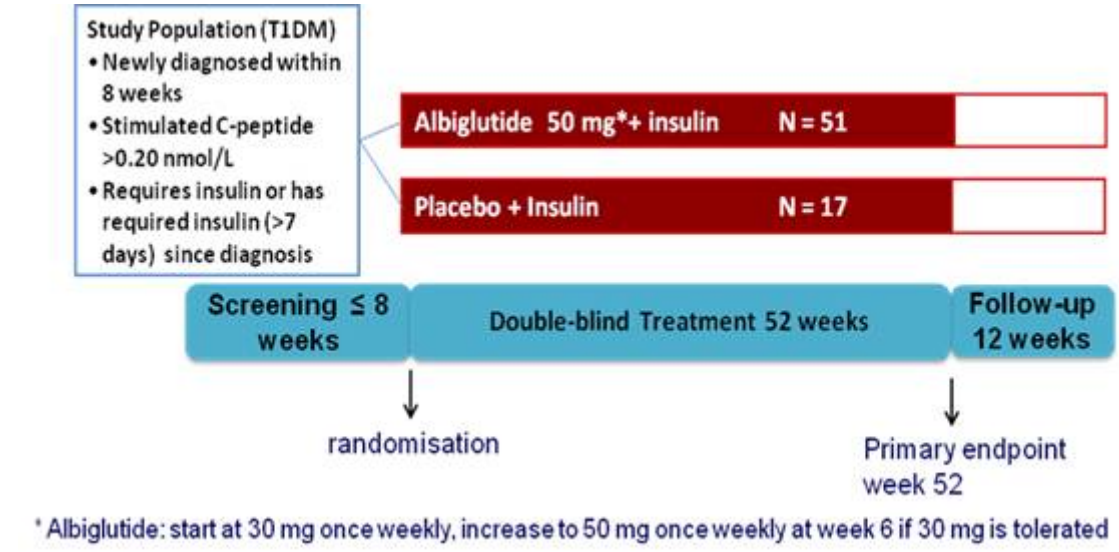
Objectives	Endpoints
• Assess the effect of albiglutide on β-cell function in the context of the prevailing glucose response to the MMTT	• β-cell function, expressed as an insulin secretion parameter, will be estimated by modelling glucose and c-peptide concentrations (as data permits). The modelling process will include, but is not limited to, the deconvolution of C-peptide data in the context of the prevailing glucose response to the meal

NOTES :

- Week 64 is an off-treatment follow-up assessment time point.
- Plasma glucagon AUC (from MMTT) is over the 2 hours of the MMTT
- All protocol endpoints are listed above, even those which will not be summarised (e.g. exploratory endpoints; population estimates of PD parameters, associated inter-subject variability and residual error if permitted by the data)

2.3. Study Design

Overview of Study Design and Key Features



Overview of Study Design and Key Features	
Design Features	• Phase II, randomised, double-blind, parallel-group, placebo controlled, multicentre study in subjects with NOT1DM. • 18-30 year old subjects, within 8 weeks of diagnosis of T1DM. • Historical data from placebo patients, aged 18-30 from the DEFEND-1 study will be incorporated into the primary endpoint analysis, using Bayesian analysis. • Key inclusion criteria: o Currently requires insulin for T1DM treatment or has received insulin at some point between date of diagnosis and first dose of study drug, o One or more positive T1DM associated auto-antibodies [i.e. positive for at least one of anti-GAD, anti-IA-2, and insulin autoantibody (IAA)]. Note: A subject who is positive for IAA and negative for the other auto-antibodies will not be eligible if the subject has been using insulin for a total of ≥7 days. o Evidence of clinically relevant residual islet β cells function (i.e., a stimulated peak C-peptide > 0.2 nmol/L during the Screening mixed meal tolerance test).
Dosing	• Albiglutide 30 mg once weekly or matching placebo with blinded increase to 50 mg once weekly at Week 6 if the 30 mg dose is tolerated. Masked down-titration from the 50 mg to 30 mg dose is permitted in cases of gastrointestinal (GI) intolerability following discussion with the medical monitor.
Treatment Assignment	• Approximately N=68 subjects randomised to albiglutide vs placebo using a 3:1 ratio • PPD statistical group generated randomisation schedules. • Centralised randomisation using PPD IVRS for treatment allocation.
Interim Analysis	• No interim analysis is planned

2.4. Statistical Hypotheses

For this Phase II, randomised, multicentre, double-blind, placebo controlled study, the primary objective is to evaluate the efficacy of albiglutide versus placebo on endogenous insulin secretion. The primary efficacy analysis endpoint will be change from baseline stimulated 2 hour MMTT C-peptide AUC at Week 52 following one year of treatment.

The primary endpoint analysis, incorporating historical placebo data from the DEFEND-1 study, will be performed using a Bayesian analysis and will therefore not utilise hypothesis testing.

However, in a non-Bayesian sensitivity analysis of the primary endpoint (excluding historical placebo data from the DEFEND-1 study) the treatment effect will be evaluated using the least squares means contrast relative to placebo. This contrast will be evaluated inferentially with a 2-sided t-test at the 0.05 criterion significance level.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.

3.2. Final Analyses

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

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. GSK have authorised unblinding of randomisation codes by PPD
5. Randomisation codes have been distributed within PPD according to PPD procedures

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat (ITT)	• Comprised of all randomised subjects who receive at least 1 dose of study medication and who have at least 1 post-baseline assessment of the primary endpoint. • This population will be based on the treatment to which the subject was randomised. • Any subject who is assigned a randomisation number by the PPD IRT system will be considered to have been randomised.	• Efficacy • Exploratory endpoints, including QoL
Safety	• Comprised of all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received (see Section 4.2).	• Study Population • Safety/tolerability • PD/Biomarkers
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a pharmacokinetic sample was obtained and analysed. • Only subjects who received albiglutide will be included in the PK population.	• PK

NOTES :

- Refer to Appendix 13: List of Data Displays which details the population to be used for each displays being generated.

DEFEND-1 Study

Subjects from the DEFEND-1 study [GlaxoSmithKline Document Number, 2011N125757_00] to be included in the Bayesian modelling for the primary analysis will be selected as follows:

- Subjects who were included in the ITT Population as defined in the DEFEND-1 RAP and study report.
- Subjects who were aged 18-30 years (inclusive). Note: Age at dosing will be used to select subjects (calculated as variable AGE in DEFEND-1 dataset).
- Subjects with non-missing values for the Baseline and Week 52 stimulated (MMTT) 2 hour plasma C-peptide AUC. LOCF values at Week 52 will be included for the DEFEND-1 study.

This selection gives the historical data from 53 placebo subjects aged 18-30 years to be included in the Bayesian analysis, as specified in the protocol for GLP110933 (stimulated 2-hour MMTT C-peptide AUC change from baseline at Week 52, mean and SD). This was based on LOCF data from DEFEND-1. The LOCF method will not be used in study GLP110933, the analysis is a repeated measures analysis. Whilst the method of handling of missing data within this analysis model is different, it was decided to use the data from DEFEND-1 as specified in the protocol (including LOCF observations), as changing to use only non-missing observed cases from DEFEND-1 would not address missing data at all.

Note: the ITT Population in DEFEND-1 was defined as all subjects who were randomised and received any part of at least 1 infusion of study drug. C-peptide AUC was calculated if there was at least one pre-MMTT sample and at least two post-MMTT samples. The population flags and derived variables from the DEFEND-1 data will be used to select the relevant subjects for inclusion as historical placebo data for the primary efficacy analysis.

Enrolled Population

For disclosure purposes, the enrolled population includes all subjects who passed screening. That is, those subjects randomised plus any subjects who passed screening but did not get assigned a treatment, e.g. a subject passed screening but withdrew consent prior to randomisation or the subject passed screening but was a run-in failure. In this study, there are no subjects who were classed as passing screening other than those who were randomised. Therefore, the enrolled population will be the same as the randomised population. The terminology ‘randomised population’ will be used in summary tables for simplicity.

4.1. Protocol Deviations

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

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

4.2. Deviations from Assigned Treatment

If a subject does not take treatment according to their randomisation, the assignment of treatment for summary and analysis will depend both on the extent of the violation and the type of data being analysed.

- If a subject takes non-randomised study treatment for only part of the study, the subject will be analysed based on the randomised treatment assignment for both safety and efficacy.
- If a subject takes non-randomised study treatment for the entire study, the subject will be analysed based on the treatment actually taken for safety analyses. However, the subject will be analysed based on randomised treatment for efficacy per the intention-to-treat principle.

4.3. Treatment Group

In this study, the dosing schedule is:

- Albiglutide 30 mg once weekly or matching placebo with blinded increase to 50 mg once weekly at Week 6 if the 30 mg dose is tolerated. Masked down-titration from the 50 mg to 30 mg dose is permitted in cases of gastrointestinal (GI) intolerability following discussion with the medical monitor.

Where data will be summarised by treatment group, this refers to the treatment regimen of albiglutide 30mg or matching placebo with blinded increase to 50mg, unless otherwise specified. That is, data will not be summarised by the dose level (30mg/50mg) unless otherwise specified i.e. certain exposure summary tables. Treatment group descriptions for reporting will be Albiglutide or Placebo (as described in Section 11.4.1).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

- Examination of subgroups: Due to the small sample size of the study and the 3:1 randomisation ratio (albiglutide:placebo), there are no planned subgroup analyses in this study.
- There are no planned adjustments made for multiple centres in this study.
- There are no planned adjustments for multiple comparisons or multiplicity.
- There is no Per Protocol Population in this study.

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
Section 11.1	Appendix 1: Time & Events
Section 11.2	Appendix 2: Assessment Windows
Section 11.3	Appendix 3: Treatment States and Phases
Section 11.4	Appendix 4: Data Display Standards & Handling Conventions
Section 11.5	Appendix 5: Derived and Transformed Data
Section 11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
Section 11.7	Appendix 7: Values of Potential Clinical Importance
Section 11.8	Appendix 8: Examination of Covariates, Subgroups & Other Strata
Section 11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
Section 11.10	Appendix 10: Population Pharmacokinetic Analyses
Section 11.11	Appendix 11: Mixed Meal Tolerance Test (MMTT) – Supplementary Information

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

Table 3 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 3 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition for the Subject Conclusion Record	Y		
Reasons for Subject Withdrawal			Y
Treatment Status and Reasons for Discontinuation of Study Treatment	Y		Y
Screening Status and Reasons for Screen Failure	Y [3]		Y [3]
Subjects Enrolled by Country and Site ID	Y [4]		
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations	Y		Y
Populations Analysed			
Study Populations	Y [3]		
Exclusions from Study Population	Y [4]		
Subjects Excluded from Any Population			Y [4]
Demographic and Baseline Characteristics			
Demographic Characteristics	Y [5]		Y
Age Ranges	Y [4]		
Race and Racial Combinations	Y		Y [1]
Substance Use	Y		Y
Demographic Characteristics for DEFEND-1 subjects	Y		Y
Medical Conditions			
Past Medical Conditions	Y		Y [6]
Current Medical Conditions	Y		Y [6]
Medical/Surgical Procedures	Y		Y
Family History of CV Risk Factors, Pancreatitis and Thyroid Cancer	Y		Y
Prior and Concomitant Medications			
Prior Medications	Y		Y [2]
Concomitant Medications	Y		Y [2]
Post-therapy Medications	Y		Y [2]
Relationship of Medication Class, Dictionary Term and Verbatim Text			Y
Exposure and Treatment Compliance			
Exposure to Study Treatment (including exposure by actual dose)	Y		
Study Treatment Titrations (Up/Down)	Y		
Compliance	Y		Y
Study Treatment Administration			Y

NOTES :

- Y = Yes display generated.
- [1] Listing of race.
- [2] Single listing of prior, concomitant and post-therapy medications combined
- [3] Based on all screened subjects
- [4] Based on all randomised subjects
- [5] Table produced for Safety, ITT and PK populations
- [6] Single listing of current and past medical conditions.

Summaries will present data for each treatment group (including 'No treatment' where applicable) and overall, unless otherwise specified.

6.1.1. Subject Disposition

The number of subjects who were screened, the number of subjects randomised and the number of subjects in each study population (ITT, Safety, PK) will be summarised.

The number and percentage of subjects excluded from each study population (ITT, Safety, PK) will be summarised. Reasons for exclusion will be presented for those subjects who were excluded from each study population. Note, this will be based on all randomised subjects.

The number and percentage of subjects randomised by country and site will also be provided. Note, this will be based on all randomised subjects.

Subject disposition will summarise the number and percentage of subjects who completed the study and who withdrew from the study. Reasons for withdrawal from the study will be presented.

A summary of the number and percentage of subjects who completed study treatment and who prematurely discontinued study treatment will be produced. Reasons for premature discontinuation of study treatment will be presented for those subjects who did not complete study treatment.

The number and percentage of subjects who were randomised and the number and percentage of subjects who failed screening and therefore were not entered into the study will be summarised. The reasons for failure will be summarised for those subjects who failed screening. Note, this will be based on all screened subjects.

6.1.2. Protocol Deviations

Important protocol deviations will be based on the protocol deviations dataset. Inclusion/exclusion deviations will be based on data recorded on the inclusion/exclusion page of the eCRF.

6.1.3. Demographics and Baseline Characteristics

The following variables will be summarised: age, sex, race, ethnicity, height, weight, body mass index (BMI), time from diagnosis of T1DM to first dose of study drug, HbA1c, C-peptide AUC, maximum stimulated C-peptide and presence of T1DM

associated antibodies (anti-GAD, anti-IA-2, and anti-insulin antibodies [IAA]). Baseline HbA1c categories and the number of positive T1DM associated antibodies (anti-GAD/anti-IA-2/IAA) each subject has (categorical) will also be presented in this summary. In addition, the number of positive T1DM associated antibodies only including anti-GAD and anti-IA-2 will be presented, in order to be consistent with information provided from DEFEND-1.

Please refer to Section 11.4.2 and Section 11.5.2 for further details on derivations and baseline definitions.

Demographic/baseline characteristics displays will be produced for all populations. If there are no differences between the ITT and safety populations, the demographic displays of these populations will be presented as one (labelled as Safety population).

Continuous variables, such as age, body mass index (BMI), and height will be summarised using descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Some variables will also be categorized, such as age and HbA1c. These and other categorical variables will be summarised by reporting the number and percentage of subjects in each category.

A separate summary of race will also be produced for subjects in the safety population, summarising data for the five high level FDA race categories and two designated Asian subcategories. As specified in GSK's IDSL Demography Statistical Display Standards document.

A separate summary of age ranges will be produced for all randomised subjects, by treatment group (including no treatment, if applicable) and overall subjects. The age ranges are standard and cannot be modified as per the EMA clinical trial results disclosure requirements. In this study the only applicable age range is Adult (18-64 years) due to the inclusion exclusion criteria. As specified in GSK's IDSL Demography Statistical Display Standards document.

DEFEND-1 Study

In order to describe the baseline characteristics of the DEFEND-1 subjects included in the primary endpoint Bayesian analysis, a summary will be produced of their demographic and baseline characteristics. This will include: age, sex, race, height, weight, body mass index (BMI), time from diagnosis to first dose of study drug, baseline HbA1c, baseline C-peptide AUC, baseline maximum C-peptide, the presence of T1DM associated antibodies (anti-GAD, anti-IA-2) and the number of positive T1DM associated antibodies (anti-GAD/anti-IA-2).

6.1.4. Medical History

Subject data listings will be provided for medical history.

A separate summary table will be provided for current medical conditions and past medical conditions. Each summary table will include the following current or past conditions:

- cardiovascular related medical conditions
- diabetes related medical conditions
- general medical conditions
- gastrointestinal (GI) and hepatobiliary medical conditions
- nephropathy (including microalbuminuria) and acute kidney injury
- thyroid condition history
- medical conditions relevant to pneumonia
- skin medical conditions
- cancer history

A summary table for medical/surgical procedure history will also be produced.

The number and percentage of subjects with current or past medical history will be reported by treatment group and overall subjects. Medical history will be collected as either pre-coded/pre-printed conditions or a verbatim (free-text) field. Pre-coded conditions will be summarised using the terms printed on the CRF. Verbatim terms are not coded and therefore can only be summarised as 'Other'.

Additional details provided for thyroid cancer and benign structural thyroid conditions will be listed.

6.1.5. Concomitant Medications

Any prior and concomitant medication used during the study will be recorded and coded using the GSK Drug coding dictionary (GSKDRUG), which will be updated whenever available throughout the life of the study. Prior medications are those started and stopped before the first dose of study drug. Concomitant medications are those taken at any time on or after the day of the first dose of study drug and within 56 days after the last dose of study drug, including those medications that were started prior to randomisation but were continued into the study period. Post-therapy medications are those started more than 56 days after the day of the last dose of study drug.

Concomitant medications will be reported by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1 (Body System) and ingredient. Drugs that are composed of a combination of ingredients will be displayed according to the ATC classifications of the ingredients, not of the combination.

6.1.6. Exposure

Please refer to Section 11.5.2 for further details of derivations.

Extent of study treatment exposure will be summarised based on duration of exposure including breaks and duration of exposure excluding breaks.

Descriptive summary statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum for the duration of study drug exposure will

be presented by treatment group. Duration of study drug exposure will also be summarised categorically. The number and percentage of subjects within each exposure category will be presented by treatment group. The total person time on treatment (in years) will also be displayed for each treatment group.

A summary of the number and percentage of subjects who did/did not achieve the forced titration (e.g. back-titrated due to lack of tolerance) will be presented. Individual dose titration information will be listed.

For albiglutide subjects, duration of exposure to study drug by actual dose level (30mg/50mg) will be summarised as described above for total duration of exposure, but presented by actual dose level (30mg or 50mg). Note, only duration of exposure including breaks will be summarised here.

Treatment compliance will be calculated for each subject, and will be summarised for all subjects, in addition to being summarised separately for patients who discontinued treatment early and patients who have completed active treatment. Summary statistics for treatment compliance (%), as well as the number and percentage of subjects who are <80% and ≥80% compliant will be reported by treatment group.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

Efficacy Analyses will be based on the ITT population and all valid efficacy assessments during the study period.

7.1.1. Overview of Planned Efficacy Analyses

Table 4 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 4 Overview of Planned Efficacy Analyses

Endpoint	Absolute							Change from Baseline [1]						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Mixed Meal Test														
Stimulated (from MMTT) 2 hour plasma C-peptide AUC [2] at Week 52				Y	Y		Y				Y	Y		Y
Stimulated (from MMTT) 2 hour plasma C-peptide AUC] at Week 52 – Primary Bayesian Analysis (w=0.5)								Y	Y	Y				
Stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 52 – Sensitivity Analysis (w=0)								Y						
Stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 52 – Sensitivity Analysis (w=1)								Y						
Stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 52 – non-Bayesian sensitivity analysis								Y						

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Absolute and change from baseline summaries combined into a single display
- [2] Displays generated using the 'ITT' population, with the exception of absolute individual listings

7.1.1.1. Overview of Planned Primary Efficacy Analyses

The primary efficacy endpoint is change from baseline in 2 hour MMTT plasma C peptide AUC at Week 52.

Primary Analysis (MMRM with Bayesian Analysis Incorporating DEFEND-1 Placebo Data) – All On-Study Data

The primary analysis of change from baseline in 2 hour MMTT plasma C-peptide AUC at Week 52 will be performed using a Bayesian analysis incorporating historical placebo data from the DEFEND-1 study using a robust mixture prior.

This is a change from the planned primary efficacy analysis specified in the protocol, where historical placebo information with 50% weight was planned to be incorporated into the Bayesian model using the SAS PROC MCMC procedure (with sensitivity analyses using 100% and 0% historical DEFEND-1 placebo data).

The following changes to the analysis specified in the protocol have also been made. The terminology referring to a 'mixed-effects' model has been removed from the description of the Bayesian analysis, as the Bayesian approach is to treat all parameters as random. The main effects of treatment group and visit will not be included in the Bayesian model as have a potential impact on likelihood of convergence. For the non-Bayesian mixed-effects model repeated measures analyses then these terms will remain in the model (as specified in the protocol), the treatment group-by-visit parameter estimates are not affected by the inclusion/removal of the main effects.

A model for change from baseline in 2 hour MMTT C peptide AUC will be used to estimate and compare the albiglutide and placebo treatment effects at Week 52. Specifically, a repeated-measures model will be fitted with change from baseline 2 hour MMTT plasma C peptide AUC as a dependant variable and baseline 2 hour MMTT C-peptide AUC, age, and treatment group-by-visit interaction as independent variables. Inclusion of the term baseline-by-visit may be considered in the final model based on model fit and/or convergence.

Age at randomisation will be used as the baseline age covariate in the model.

Historical placebo data (from 53 subjects aged 18-30 years from the DEFEND-1 study) will be incorporated into the Bayesian model using SAS Markov chain Monte Carlo procedure (PROC MCMC) and the following robust mixture prior [Schmidli, 2014].

w (Historical prior) + (1 - w) (weakly informative prior)

where:

Historical prior = prior historical data from a single study,

weakly informative prior is Normal with large variance,

w is how robust the prior is considered to be e.g. w=0 is pure weakly informative prior; w=1 is the historical prior.

The weighting of the DEFEND-1 placebo data depends on its similarity to the GLP110933 study placebo data. The mixture prior down-weights the historical data when the historical data does not agree with the GLP110933 study placebo data. The mixture prior up-weights the historical data when the historical data agrees with the GLP110933 study placebo data. The choice of w determines how quickly historical information is discounted as prior-data conflict increases. The primary analysis will use a w value of 0.5; this corresponds to the choice of 50% weighting for the primary analysis as planned in the protocol.

The model will use a general (unstructured) covariance matrix as specification for the covariance among observations from the same subject. The model will provide an unbiased treatment difference estimate for the Week 52 time point, with better precision

achieved by accounting for intra subject variability than an analysis of covariance approach. In the event of missing observations at Week 52, the planned analysis and test are valid under a "missing at random (MAR)" assumption where missing data may depend on prior observations.

This Bayesian analysis will derive the posterior distribution for the C-peptide treatment difference (Albiglutide – placebo), which will be plotted and an estimate of the treatment difference (median) and 95% (highest posterior density (HPD)) credible interval will be produced, together with the construction of the following probability statements:

- probability that the treatment difference >= 0.2 nmol/L (clinically relevant "good effect")
- probability that the treatment difference is >= 0.1 nmol/L (clinically relevant "some effect")
- probability that the treatment difference >= 0 nmol/L ("no effect").

Sensitivity Analysis (MMRM with weighting of 0% and 100% DEFEND-1 Placebo Data) – All On-Study Data

Sensitivity analyses will be performed for the primary Bayesian analysis using PROC MCMC, repeating the analysis described above but using the following values for w:

- w=0; corresponding to without historical placebo data.
- w=1; corresponding to 100% historical placebo data.

Non-Bayesian Sensitivity Analysis (MMRM) – All On-Study Data

As a further sensitivity analysis, a non-Bayesian repeated measures mixed effect model using PROC MIXED will be fitted, using all valid efficacy assessments during the study period. This model will not include any historical placebo data from the DEFEND-1 study. This analysis will be performed using the MMRM approach, as described for the secondary endpoints in Section 8.1.2 (change from baseline in stimulated (from MMTT) 2 hour plasma C-Peptide AUC at Week 16, 28 and 64). For this analysis only:

A test of the treatment group difference at Week 52 will be provided by the comparison of the appropriate treatment group-by-visit least square means (LS means).

The difference will be considered significant if the two sided p-value for the comparison between treatments in change from baseline 2 hour MMTT C-peptide AUC is less than or equal to 0.05. The corresponding 95% confidence intervals will also be presented.

Additional sensitivity analyses are described in Section 7.1.2.

The details regarding MMTT assessments are provided in Section 11.11.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Change from Baseline in stimulated 2 hour plasma C-peptide AUC (from MMTT) at Week 52

Model Specification

- Endpoints will be statistically analysed using a mixed models repeated measures (MMRM) model and Markov chain Monte Carlo (MCMC) procedure and a robust mixture prior.
- Terms fitted in the MMRM model will include:
- Dependent variable : Change from Baseline
- Categorical : Treatment-by-Visit Interaction
- Continuous Covariates : Baseline, Age (years)
- The model will use a general (unstructured) covariance matrix as specification for the covariance among observations from the same subject.
- Inclusion of the term baseline-by-visit may be considered in the final model based on model fit and/or convergence.
- All post-baseline scheduled visits will be included in the analysis using nominal visit.
- To model within-subject covariance structures, the input dataset should have all repeated measure from a subject in one row. A multivariate normal (MVN) distribution will be specified in the MODEL statement to model all repeated measurements within the same subject. The MVN distribution can only be applied to array-based variables. The model statement will include arrays for the response variables, and arrays which are the means and covariance matrices of the likelihood function.
- The likelihood function will be specified using the MODEL statement
- Programming statements will be used to define the model within PROC MCMC
- Parameters in the model will be declared using the PARMS statement
- The prior distributions will be specified using the PRIOR statements
- For the Bayesian analysis only, the continuous covariates (baseline and age) will be centered for use in PROC MCMC. For baseline, the mean baseline overall treatment groups will be calculated and this overall mean value will be subtracted from each subjects' individual baseline value. This 'centered baseline' will be used as the covariate in the model. A similar calculation will be performed for age (years). This often helps model convergence and reduces correlation between regression parameters.
- In order to assess convergence and make inferences, three Markov chains will be run and the Gelman & Rubin diagnostic will be determined by using the SAS provided macro %GELMAN. To run three chains, PROC MCMC needs to be called three times with different starting values for SEED and initial parameter values. The values to be used are:
    - Chain 1: SEED=127856, initial parameter values: centered age -5, week 52 placebo -0.35, and for centered baseline, other placebo visits and all albiglutide visits -0.3.
    - Chain 2: SEED=334912, initial parameter values: centered age 0, week 52 placebo -0.25, and for centered baseline, other placebo visits and all albiglutide visits 0.
    - Chain 3: SEED=928651, initial parameter values: centered age 5, week 52 placebo 0, and for centered baseline, other placebo visits and all albiglutide visits 0.3.

Primary Statistical Analyses

  - Note: the initial parameter values will be used for all parameters in the model (as specified above) with the exception of the covariance matrix of the likelihood function which will use SAS default initial parameters for all chains.

- Initially each chain will run with a simulation size of 50000 (NMC=50000) and all three chains will be included to provide the posterior distribution summaries, treatment differences and construct probability statements (i.e. using a total of 150000 posterior observations).
- SAS provided macros, including %POSTSUM, %TADPLOT and %POSTINT, will be used to provide summaries of the posterior distribution (including 95% HPD credible intervals).
- Thinning will not be used (THIN=1)
- Initially the SAS default of 1000 iterations will be used for the number of burn-in's (NBI=1000)
- For tuning, the following values will be specified: MINTUNE=5, MAXTUNE=500 and NTU=2000.
- Convergence will be assessed using the Gelman & Rubin diagnostic, examining trace plots for model parameters, assessing the Effective Sample Size (ESS) and Geweke diagnostics. The ratio of the Monte Carlo Standard Error (MCSE) to the SD of the posterior will also be assessed. If the model does not converge then the number of burn-in's (NBI), the number of simulations (NMC) and the tuning values may be adjusted, as appropriate, in order to improve model convergence. The numbers by which MCMC iterations and burn-in iterations need to be increased may be significant. Additional adjustments to the model may be necessary if convergence is not improved.
- Historical placebo data from 53 subjects from the DEFEND-1 study will be incorporated as the prior distribution for the Week 52 visit using the robust mixture prior as follows:
  - From DEFEND-1, N = 53 and the mean change from baseline was -0.269, SD = 0.314 and SE = 0.043.
  - The historical prior will be specified as Normal (-0.269, SE=0.043)
  - The weakly informative prior will be specified as Normal (0, SE=1000);
  - Iprior = log [w * pdf (historical prior) + (1-w) * pdf (weakly informative prior)]
  - Prior (week 52 placebo) ~ General (Iprior)
- Priors for other parameters (including placebo at other visits) will be specified as Normal (0, var=1E6)

Model Checking & Diagnostics

- Convergence of the Bayesian model will be assessed as described above.

Model Results Presentation

- A model-adjusted estimate of the change from baseline for will be presented for each treatment group, including the posterior median, posterior SD, and 95% highest posterior density (HPD) credible interval.
- An estimate of the treatment difference and 95% credible interval will be produced, together with the construction of the following probability statements:
  - probability that the treatment difference >= 0.2 nmol/L (clinically relevant "good effect")
  - probability that the treatment difference is >= 0.1 nmol/L (clinically relevant "some effect")
  - probability that the treatment difference >= 0 nmol/L ("no effect").
- A plot of the distribution of the C-peptide treatment difference (Albiglutide – placebo) will be produced.

Primary Statistical Analyses
Summary TFLs
• Summary statistics for baseline, absolute and change from baseline at Week 52 will be presented for the placebo group and the historical DEFEND-1 placebo group.

Sensitivity and Supportive Statistical Analyses
• Sensitivity analyses will be performed without historical DEFEND-1 placebo data and using 100% historical DEFEND-1 placebo data. • The analyses will be performed as described for the primary Bayesian analysis, however the robust mixture prior will use values of w=0 and w=1 respectively, rather than w=0.5 (primary analysis).
• As a further sensitivity analysis, a non-Bayesian repeated measures mixed effect analysis using PROC MIXED will be performed. This model will not include any historical placebo data from the DEFEND-1 study. The analysis will be performed using the MMRM approach, as described for the secondary endpoints in Section 8.1.2 (change from baseline in stimulated (from MMTT) 2 hour plasma C-Peptide AUC at Week 16, 28 and 64)
• If the amount of missing data is large, the potential impact of missing follow-up data on the conclusions of the primary analysis will be investigated through sensitivity analyses. For example, for each treatment group, the baseline characteristics of the subjects whose Week 52 mixed meal-stimulated C-peptide AUC is missing will be compared with those subjects with available Week 52 mixed meal-stimulated C-peptide AUC data to provide an assessment of the potential for the missing data to cause bias in the conclusions. The report will include presentation of the results of the sensitivity analysis, and a discussion of the implications of both the sensitivity analysis and the comparisons of baseline characteristics on interpreting the conclusions from the primary hypothesis test.

Possible Post-hoc Sensitivity Statistical Analyses: The following sensitivity analyses are not currently planned to be performed, but may be performed as post-hoc sensitivity analyses if needed
• A sensitivity analysis based on 'on-treatment' observations only may be performed for the primary endpoint Bayesian analysis only (MMRM, MCMC procedure and robust mixture prior). • For the historical DEFEND-1 placebo data, 'on-treatment' will not be assigned and all previously selected data will be included in the sensitivity analysis. This is due to the fact that the treatment period for DEFEND-1 was only 8 infusions over 8 days at the start of the study. • For GLP110933, 'on-treatment' data is defined as: Study Treatment Start Date < Date ≤ Study Treatment Stop Date. If this post-hoc analysis is performed, the timing of MMTT assessments versus treatment stop dates will be explored to ensure as much data as possible would be included in the analysis (i.e., the definition of the on-treatment period may be extended slightly from date of last dose)
• In addition to the treatment comparisons described above, there may be a test for treatment group by time (continuous) interaction in the model (adjusted for baseline value and age). • A significant interaction would indicate that the treatment difference in 2 hour MMTT C-peptide AUC between groups varies over time to a greater degree than expected by chance. • If there is no evidence of an interaction at the 0.05 level of significance, then the overall treatment group LS means (across all time points) would be reported. • This analysis would be performed using the MMRM model described in Section 8.1.2 (change from baseline in stimulated (from MMTT) 2 hour plasma C-Peptide AUC at Week 16, 28 and 64), however replacing the categorical visit variable with a continuous time variable.
• An additional analysis of interest may be performed to examine the C-peptide AUC data for a trend over time. To assess this, a mixed-effects model would be specified with a linear trend after Week 28 to describe the mean rate of change (decrease) within treatment groups over time. To allow for an acute effect on C-peptide as observed in other studies, the baseline value would be entered as a covariate (not as one of the repeated measures over time); time would then be rescaled such that Time 0 is the first post-treatment C-peptide value, i.e., that at Week 16. The mixed-effects model would be specified with baseline C-peptide AUC, treatment group, and age as fixed effects. Between-subject differences in change from baseline AUC and treatment effect over time would be handled by specification of random effects for intercept and slope (time), respectively. The treatment group fixed effect would test the difference between groups in the mean intercepts (means at Week 16), and the treatment group-by-time interaction effect would test for differences between slopes over the period from Week 28 through Week 52. A general (unstructured) covariance matrix would be specified for the covariance among observations from the same subject.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the "Intent-To-Treat" population, unless otherwise specified.

Table 5 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 5 Overview of Planned Efficacy Analyses

Secondary Efficacy Endpoints	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Mixed Meal Tolerance Test (Baseline, Week 16, 28, 52, 64)														
Stimulated (from MMTT) 2 hour plasma C-peptide AUC [3]				Y[1]	Y		Y	Y			Y[1]	Y		Y
Plasma Glucagon AUC (from MMTT)				Y[1]	Y		Y	Y[4]			Y[1]			Y
Maximum plasma C-peptide during 2hr MMTT				Y[1]	Y		Y	Y[4]			Y[1]			Y
Percent of Responders (Baseline, Week 4, 8, 16, 28, 40, 52 and 64)														
HbA1c ≤7.0 and insulin dose<0.5 units/kg/day	Y[4]			Y	Y		Y							
IDAA1C ≤9	Y[4]			Y	Y		Y							
Glucose Control (Baseline, Week 4, 8, 16, 28, 40, 52 and 64)														
HbA1c				Y[1]	Y		Y	Y[4]			Y[1]			Y
Mean daily insulin dose				Y[1]	Y		Y	Y[4]			Y[1]			Y
Subject-Reported Hypoglycaemic Events														
Number of hypoglycaemias with confirmed plasma glucose monitoring ≤3.9 mmol/L and/or requiring third party intervention occurring >Week 24 and ≤Week 52				Y[2]			Y							

Secondary Efficacy Endpoints	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
7-Point Glucose Profile														
Glucose levels at each of the 7 specified time-points of the 7-point glucose profile at Baseline, Week 28 and Week 52				Y										
Number of hypoglycaemic excursions (≤3.9 mmol/L) from 7-point glucose profile				Y										
Proportion of subjects with hypoglycaemic excursions from 7-point glucose profile				Y										
Greatest magnitude of hypoglycaemic excursion from 7-point glucose profile				Y										
Number of hyperglycaemic excursions (>10 mmol/L) from 7-point glucose profile				Y										
Proportion of subjects with hyperglycaemic excursions from 7-point glucose profile				Y										
Greatest magnitude of hyperglycaemic excursion from 7-point glucose profile				Y										
Listing of data from 7-point glucose profile							Y							
72-hr CGM (Baseline, Week 28, 52)														
Proportion of time spent with plasma glucose ≤3.9 mmol/L; between >3.9 and 10.0 mmol/L; and >10.0 mmol/L				Y[1]	Y		Y	Y[4]			Y[1]	Y		Y
Weight (Baseline, Week 2, 4, 6, 8, 16, 28, 40, 52 and 64)														
Body weight (kg)				Y[1]	Y		Y	Y[4]			Y[1]			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Absolute and change from baseline summaries combined into a single display
- [2] Summary table will also be produced for the Baseline to Week 24 time-period.
- [3] MMTT C-peptide AUC: week 52 time-point is the primary efficacy endpoint, refer to Section 7 for details of statistical analysis.
- [4] Statistical analysis performed at Week 28 and Week 52 only

8.1.1.1. Supplementary Information for Subject-Reported Hypoglycaemic Events

Subject-reported hypoglycaemic events (see Section 11.5.3 and Section 11.5.4) will be used for this endpoint. This endpoint will determine any differences in significant hypoglycaemia (i.e., events with plasma glucose ≤3.9 mmol/L and/or requiring third party intervention); that is severe, documented symptomatic and asymptomatic hypoglycaemic events as defined by ADA category.

Incidence of severe hypoglycaemia, documented symptomatic hypoglycaemia, and asymptomatic hypoglycaemia will be tabulated by treatment group. Incidence is defined as the numbers of subject-reported hypoglycaemic events per subject, and total percentages of subjects affected. The summary table will present the average number of events per subject (i.e. the number of subject reported hypoglycaemic events divided by the number of subjects), incidence (percentages of subjects affected) and the number of events occurring by treatment group. The summary will be produced for the time period from Baseline to Week 24, and from > Week 24 to ≤Week 52.

Further exploratory analysis may be done, depending on the amount of missing data.

8.1.1.2. Supplemental Information for Plasma Glucagon (from MMTT)

There was a change to the lower limit of quantification for the plasma glucagon test at the laboratory during the course of the study. This would be an issue at the individual subject level if the lower limit at the baseline visit was different to the lower limit used for subsequent visits. Further explanation and details on how this will be handled can be found in Section 11.5.4.

8.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses

Endpoint(s)

- Change from baseline in stimulated (from MMTT) 2 hour plasma C-Peptide AUC at Week 16, 28 and 64
- Change from baseline in maximum stimulated plasma C-Peptide at Week 28 and 52
- Change from baseline in plasma glucagon AUC (from MMTT) at Week 28 and 52
- Change from baseline in HbA1c (%) at Week 28 and 52
- Change from baseline in mean daily insulin use at Week 28 and 52
- Change from baseline in body weight (kg) at Week 28 and 52

Model Specification

- Endpoints will be statistically analysed using a mixed models repeated measures (MMRM) model, using PROC MIXED in SAS.
- All post-baseline scheduled visits will be included in the analysis (as appropriate to the endpoint) using nominal visit. [Including Week 52 for C-peptide AUC]
- The mixed effects model will use a general (unstructured) covariance matrix as specification for the covariance among observations from the same subject.
- A test of the treatment group difference at each visit will be provided by the comparison of the appropriate treatment group-by-visit least square means (LS means).
- Terms fitted in the MMRM model will include:
  Dependent variable: Change from Baseline
  Fixed categorical: Treatment, Visit, Treatment-by-Visit Interaction
  Fixed Continuous Covariates: Baseline, Age (years)
  Repeated Effect: Visit with Subject as the blocking variable
  Covariance Matrix: General (Unstructured) #
  # If the model fails to converge, a less stringent correlation matrix will be specified – to be decided based upon model convergence status and Akaike information criteria (AIC)
- Inclusion of the term baseline-by-visit may be considered in the final model based on model fit and/or convergence.
- Model parameter estimates will be computed estimates will be computed by the restricted maximum likelihood (REML) method.
- The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for tests.

Model Checking & Diagnostics

- Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Least squares means and corresponding standard error of means (SEs) for change from baseline will be presented for each treatment group at each time-point.
- The estimated treatment difference, associated 95% confidence interval and p-value will be presented at each time-point.

Secondary Statistical Analyses

Summary TFLs

- Summary statistics for absolute and change from baseline will be presented for each treatment group at all visits (including visits with no statistical analysis performed)
- For C-peptide AUC, plots of mean absolute (± SE) and mean change from baseline (± SE) will be presented for each treatment group over time
- For other endpoints, plots of mean absolute (± SE) will be presented for each treatment group over time
- Data will be listed.

HbA1c

- Statistical analysis of HbA1c will be performed using HbA1c in units of %.
- Summary statistics for absolute and change from baseline will be presented in units of % and in units of mmol/mol
- Plots will be presented using units of %
- Data listings will contain both units of % and units of mmol/mol

Endpoint(s)

- Percentage of Responders (defined as subjects with HbA1c ≤7.0 and mean daily insulin use <0.5 units/kg/day) at Week 28 and 52
- Percentage of subjects achieving partial remission status (i.e., insulin dose-adjusted haemoglobin A1c [IDAA1C] ≤9.0) at Week 28 and 52

Model Specification

- The treatment comparison will be undertaken with a non-parametric, covariance-adjusted, extended Mantel-Haenszel test using the SAS FREQ procedure.
- Age (categorical) will be included as a covariate.
- This technique is especially suited for situations in which covariance adjustment is needed to optimise statistical power, while minimizing the modeling assumptions.

Model Checking & Diagnostics

- Not applicable

Model Results Presentation

- The odds ratio, associated 95% confidence interval and p-value for the treatment difference will be presented at each time-point.

Additional Covariate Information

- In this analysis, age will be included as a categorical covariate. Age will be dichotomised into a binary variable, based on whether a subject's age is above or below the median age (overall subjects in the ITT population).
- Age categories: < median age (years); ≥ median age (years)

Missing data

- In a change from the planned analysis, the LOCF method will not be used for HbA1c and insulin usage. All available data will be used for the analysis.
- A post-hoc sensitivity analysis imputing missing data may be performed if needed, but is not currently planned to be performed. If a subject has missing HbA1c/insulin use data and the reason why the value is missing is not related to efficacy or safety (e.g., procedural) and could be assumed that the value is missing at random, then the value would be left as missing for calculations; if the reason why the value is missing is lack of efficacy or due to safety, then this missing value would be imputed as 'not meeting target' and included in the denominator in the calculations of the proportion of responders. See Section 11.6.2.2 for further details.

Secondary Statistical Analyses
Summary TFLs
Responders/Partial Remission: • The proportion of responders (number and percentage) will be presented for each treatment group at all visits (including visits with no statistical analysis performed). • The proportion of responders over time will be presented graphically for each treatment group. • Data will be listed.
Endpoint(s)
• Number of events of hypoglycaemia with confirmed self plasma glucose monitoring ≤3.9 mmol/L and/or requiring third party intervention (i.e. severe, documented symptomatic and asymptomatic hypoglycaemic events) occurring >Week 24 and ≤Week 52. • Number and magnitude of hypoglycaemic (≤3.9 mmol/L) excursions from the 7-point glucose profile at Baseline, Week 28 and Week 52 • Number and magnitude of hyperglycaemic (>10.0 mmol/L) excursions from the 7-point glucose profile at Baseline, Week 28 and Week 52
Model Specification
• Formal comparative statistical analysis will not be performed for these endpoints.
Model Checking & Diagnostics
• Not applicable.
Model Results Presentation
• Not applicable.
Summary TFLs
Subject-Reported Hypoglycaemic Events: • For the time periods (Baseline to Week 24; >Week 24 ≤Week 52): the average number of significant events per subject (i.e. number of subject-reported events divided by the number of subjects); percentage of subjects reporting significant events; and the total number of significant events; will be presented for each treatment group. • Data will be listed. **7-point glucose profile:** • The glucose level at each of the 7 specified timepoints of the 7-point glucose profile will be summarised for each treatment group using descriptive summary statistics. • The number and percentage of subjects with any hypoglycaemic excursions will be presented for each treatment group. • The number of hypoglycaemic excursions that each subject experienced will be summarised for each treatment group using descriptive summary statistics. • The greatest magnitude of hypoglycaemic excursion of each subject will be summarised for each treatment group using descriptive summary statistics • The summaries will be repeated for hyperglycaemic excursions. • Data will be listed.
Endpoint(s)
• Proportion of time spent with plasma glucose ≤3.9 mmol/L; between >3.9 and 10.0 mmol/L; and >10.0 mmol/L (72h CGM) at Baseline, Week 28 and Week 52.

Secondary Statistical Analyses
Model Specification
• Change from baseline in time spent (h/day) with plasma glucose ≤3.9 mmol/L at Week 28 and Week 52; • Change from baseline in time spent (h/day) with plasma glucose between >3.9 and 10.0 mmol/L at Week 28 and Week 52; • Change from baseline in time spent (h/day) with plasma glucose >10.0 mmol/L at Week 28 and Week 52; • Statistical analysis will be performed separately for the 3 endpoints, however care should be taken when interpreting results as due to the nature of the endpoints the data is linked. • The endpoints will be statistically analysed using separate mixed models repeated measures (MMRM) models, using PROC MIXED in SAS. • The analysis will be performed as described for the secondary endpoints using the MMRM methodology.
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses. • Due to the correlation between the 3 endpoints, a multivariate (MANOVA) approach may additionally be explored.
Model Results Presentation
• Least squares means and corresponding standard error of means (SEs) for change from baseline will be presented for each treatment group at each time-point. • The estimated treatment difference, associated 95% confidence interval and p-value will be presented at each time-point.
Summary TFLs
• The proportion of time spent with plasma glucose ≤3.9 mmol/L; between >3.9 and 10.0 mmol/L; and >10.0 mmol/L will be presented for each treatment group at Baseline, Week 28 and Week 52 using descriptive statistics. Results presented in both hours/day and %. • Change from baseline in the proportion of time spent with plasma glucose ≤3.9 mmol/L; between >3.9 and 10.0 mmol/L; and >10.0 mmol/L will be presented for each treatment group at Week 28 and Week 52 using descriptive statistics. Results presented in both hours/day and %. • A pie chart will be presented for each treatment/visit showing the mean hours/day spent in each of the 3 plasma glucose categories. • A bar chart will be presented for each of the 3 glucose categories showing the change from baseline in the mean hours/day spent in that plasma glucose categories for each treatment group at Week 28 and Week 52. Results presented as %. • Data will be listed, including time spent in each of the 3 plasma glucose categories.

8.2. Safety Analyses

8.2.1. Overview of Planned Adverse Events Analyses

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

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 6 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
Overview of AEs	Y		
All AEs by SOC and PT	Y [2]		Y
Common AEs by Overall Frequency	Y [3]		
Drug-Related AEs by SOC and PT	Y [2]		
All AEs by SOC and PT and Maximum Intensity	Y [2]		
Drug-Related AEs by SOC and PT and Maximum Intensity	Y [2]		
Common Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y [3]		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT and Verbatim Text			Y
Serious and Other Significant AEs			
Serious AEs	Y [1]		
Reasons for Considering as a Serious AE			Y
Drug-Related Serious AEs [9]			
Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y [3]		
Fatal Serious AEs [9]			Y
Drug-Related Fatal Serious AEs [9]			
Non-Fatal Serious AEs [9]			Y
Drug-Related Non-Fatal Fatal Serious AEs [9]			
AEs Leading to Permanent Discontinuation of Study Treatment by SOC and PT	Y [3]		Y
AEs Leading to Withdrawal from Study by SOC and PT	Y [2]		Y
Other Significant AEs [7]			
AEs of Special Interest			
Overview of Adverse Events of Special Interest	Y [3]		
Investigator-Reported Cardiovascular Events by SOC and PT	Y [3]		Y
Investigator-Reported Atrial Fibrillation/Atrial Flutter by SOC and PT	Y [3]		Y
Subject-Reported Hypoglycaemic Events by ADA category in 3-monthly Intervals	Y [6]		
Subject-Reported Hypoglycaemic Events with plasma glucose <3.1 mmol/L	Y [6]		
Subject-Reported Daytime/Nocturnal Hypoglycaemic Events by ADA category	Y [6]		
Subject-Reported Hypoglycaemic Events over Time	Y [6]	Y [6]	
Subject-Reported Hypoglycaemic Events			Y
Investigator-Reported Pneumonia Events by SOC and PT	Y [3]		Y
Investigator-Reported Pancreatitis Events by SOC and PT	Y [3]		Y

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Positively Adjudicated Pancreatitis Events by SOC and PT	Y [3]		
Investigator-Reported Thyroid Adverse Events by SOC and PT	Y [3]		Y
Gastrointestinal (GI) Events by SOC and PT	Y [3]		
GI Events Over Time [4]	Y [3]		
Summary of Characteristics of Events [5]	Y [3]		
Investigator-Reported Investigational Product Injection Site Reactions by SOC and PT	Y [3]		Y
Summary Characteristics of Investigator-Reported Investigational Product Injection Site Reactions	Y [3]		
Summary Characteristics of Investigator-Reported Investigational Product Injection Site Reactions by Anti-Albiglutide Antibody Status	Y [3]		
Investigator-Reported Systemic Allergic Reactions	Y [3]		Y
Liver Monitoring/Stopping Event Reporting	Y [8]		Y
Liver Events (Customised MedDRA Query) by SOC and PT	Y [3]		Y
Investigator-Reported Renal Impairment by SOC and PT	Y [3]		Y
Diabetic Ketoacidosis (DKA) by SOC and PT	Y [3]		Y
Appendicitis by SOC and PT	Y [3]		Y
Pancreatic Cancer by SOC and PT	Y [3]		Y
Malignant Neoplasms by SOC and PT	Y [3]		Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Produced for the pre-therapy, on-therapy and post-therapy phases separately.
- [2] Produced for the on-therapy and post-therapy phases separately.
- [3] Produced for the on-therapy phase only.
- [4] Produced for any GI event
- [5] Produced for Diarrhoea, Nausea, and Vomiting
- [6] Includes all events, on-therapy and post-therapy combined.
- [7] There are no other significant adverse events identified in this study; however AEs of special interest have been defined.
- [8] Combined on-therapy and post-therapy summary table.
- [9] Due to the low number of serious AEs reported, summary tables will not be produced for these events.

8.2.1.1. Adverse Events

Adverse events will be categorized by their occurrence in regard to therapeutic phase (pre-therapy, on-therapy, or post-therapy) as defined in Section 11.3.2.1.

All AEs will be coded using MedDRA, with MedDRA version updates throughout the study when available. In general, AEs will be presented in descending order starting with the system organ class (SOC) with the highest total incidence (that is, summed across all treatment groups) for any adverse event within the class, to the SOC with the lowest total incidence. Within each SOC level, AEs will be presented in descending order from the MedDRA preferred term (PT) with the highest total incidence to the PT with the lowest

total incidence. If the total incidence for any two or more PTs within an SOC is equal, the PTs will be presented in alphabetical order. A PT will not be presented if no adverse events occur within the level.

Only hypoglycaemic events which met the definition of an SAE were to be reported as adverse events. Any hypoglycaemic events reported as an AE will included in the adverse event summary tables. Hypoglycaemic events will be reported separately (see Section 8.2.1.7.3).

An overview summary of the number and percentage of subjects with any AE, the total number of AEs recorded, and the overall AE density for on-therapy AEs (defined in Section 11.5.3) will be provided by treatment group. The overview will also summarise SAEs (including fatal, non-fatal and drug-related), drug-related AEs, AEs leading to discontinuation of study treatment and/or withdrawal from the study, AEs by maximum intensity, and AEs by therapy phase. This summary will include all AEs from the pre-therapy, on-therapy and post-therapy phases. The summary table will indicate if the drug-related AEs are related to blinded study medication (albiglutide/placebo) or insulin.

If any AE summary table does not contain any adverse events, then the summary table will be produced with a statement indicating that there are no adverse events to report.

8.2.1.2. Drug-Related Adverse Events

Drug-related summary tables will be produced for AEs related to blinded study medication (albiglutide/placebo) only. No summaries will be produced for AEs related to insulin. This definition applies throughout the AE section, when drug-related events are mentioned. See Section 11.5.3 for further details.

If a relationship to the study drug is missing or unknown after the start of treatment it will be assumed, for the purpose of analyses, to be drug-related (to blinded study medication).

8.2.1.3. Adverse Events by Maximum Intensity

Subjects who experience the same event several times, with different intensity, will only be counted once according to the maximum intensity experienced (for that therapeutic phase). AEs with missing intensity will be considered to be severe for the purposes of summarisation.

8.2.1.4. Most Common Adverse Events

A summary of most common on-therapy adverse events (≥6% in any treatment arm) by treatment will be produced, presented by PT only (no SOC).

In addition, a summary of most-common on-therapy non-serious AEs (with ≥5% incidence in any of the treatment groups) will be summarised by treatment group following government clinical register format. As specified in GSK's IDSL Adverse Event Statistical Display Standards document.

8.2.1.5. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarised. SAE data will be categorized and presented in a manner similar to that described for the general AE summaries (except presented by PT only, no SOC) by treatment group for pre-therapy, on-therapy, and post-therapy phases.

A summary of the number and percentage of subjects and the number of occurrences of serious, drug-related serious, fatal serious, and drug-related fatal serious adverse events will be created for disclosure requirements to regulatory agencies. The events will be grouped by SOC and PT in a similar manner to that described above for general AE summaries. The summary will be presented for the on-therapy phase.

Data listings will be presented for fatal SAEs and non-fatal SAEs. Due to the low number of SAEs reported in this study, summary tables for other SAE categories (e.g., drug related SAEs, fatal SAEs) will not be produced. The data listings will be used to identify these events.

8.2.1.6. Adverse Events Leading to Permanent Discontinuation of Investigational Product and/or Withdrawal from the Study

The overview of AEs will show the number of subjects with AEs leading to permanent discontinuation of study treatment and/or withdrawal from the study. However individual summary tables by SOC and PT will be produced for AEs leading to permanent discontinuation of study treatment (on-therapy phase), and AEs leading to withdrawal from the study (on-therapy and post-therapy phase separately).

8.2.1.7. Adverse Events of Special Interest

An overview summary of the number and percentage of subjects and the total number of AEs will be presented for: any AE of special interest (AESI); any serious AESI; any drug-related AESI; and any AESI leading to discontinuation of study treatment. The corresponding AE density will be presented for each on-therapy AESI. This summary will present results for each AESI by treatment group.

For any AEs of special interest, if the number of events is limited and does not warrant a summary table, then only by subject data listings will be provided.

AESI summary tables will present on-therapy AEs; AESI listings will present data from all therapy phases, and will include a flag to identify the therapy phase.

By-subject data listings will be provided for all AESI's, with the exception of Gastrointestinal Events (where information can be found within the main adverse event listing). The sections below indicate where AESI's have additional information collected on other eCRF pages, which will also be listed.

8.2.1.7.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias including atrial fibrillation/flutter
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

Cardiovascular events are reported by the Investigator on specific eCRFs for each event. These events are not adjudicated.

8.2.1.7.2. Atrial Fibrillation/Atrial Flutter

In addition to being included within the cardiovascular event 'arrhythmias' above, atrial fibrillation/atrial flutter events are also reported by the Investigator on a specific atrial fibrillation/atrial flutter eCRF.

8.2.1.7.3. Subject-Reported Hypoglycaemic Events

Subject-reported hypoglycaemia summaries include on-therapy and post-therapy events.

Hypoglycaemic events are reported in a subject eDiary; any meeting the SAE criteria are also reported in the adverse event data. The following summaries use subject-reported data (see Section 11.5.3). Incidence will be reported using the number and percentage of subjects experiencing events and the number of events.

Incidence of hypoglycaemia (in total and by each category as defined by ADA criteria) overall and in 3 monthly intervals will be summarised by treatment group.

Incidence of daytime hypoglycaemia (in total and by ADA category) and nocturnal hypoglycaemia (in total and by ADA category) will be summarised by treatment.

Incidence of hypoglycaemia with plasma glucose <3.1 mmol/L (< 56mg/dL), regardless of symptoms, will be summarised by treatment.

The number and percentage of subjects reporting hypoglycaemia during each two week period will be presented by treatment group. A summary table and plot will be produced. In addition, the number of hypoglycaemic events reported per subject during each two week period will be presented by treatment group. A summary table will be produced, and the mean number of hypoglycaemic events reported per subject during each two week period will be plotted.

Further exploratory analysis may be done, depending on the amount of missing data.

A by-subject listing of all subject-reported hypoglycaemic events will be produced.

Note: subject-reported hypoglycaemic events are also summarised as part of the secondary efficacy endpoints.

8.2.1.7.4. Pneumonia

Pneumonia events are reported by the Investigator on a specific pneumonia eCRF.

8.2.1.7.5. Pancreatitis (Investigator-reported/Adjudicated)

A by-subject listing of all the data elements collected on the pancreatitis eCRF pages will be presented for subjects who experienced pancreatitis (including the pancreatitis, abdominal ultrasound, abdominal CT scan, MRI and additional information forms). This listing of the pancreatitis events will also include the adjudication results as determined by the independent pancreatitis adjudication committee (PAC).

8.2.1.7.6. Thyroid Adverse Events

Thyroid adverse events are reported by the Investigator on a specific thyroid cancer, nodule or goiter diagnosis eCRF.

8.2.1.7.7. Gastrointestinal (GI) Events

A summary of the number and percentage of subjects with GI events (specifically, AEs coded to the MedDRA SOC of gastrointestinal disorders) will be reported by treatment group.

The number and percentage of subjects reporting any GI event at each study week will be presented by treatment group. Each week will include those subjects with onset of a GI event during that particular week and also those subjects with a GI event that started during a previous week but has not resolved.

Various characteristics of nausea, vomiting and diarrhoea will be summarised, separately.

8.2.1.7.8. Injection Site Reactions

Investigational product injection site reactions are reported by the Investigator on a specific injection site reaction eCRF.

Various characteristics of injection site reactions (like intensity, duration, size, outcome, action taken, onset relative time to the first and preceding dose, relationship to IP, number of events and symptoms) at the event level and subject level will be summarised. The number and percentage of subjects categorized by total number of injection site reactions (1, 2, 3 to 5, 6 to 10, 11 to 20, or >20 events) will also be provided.

A summary table of characteristics of injection site reactions will also be presented by anti-albiglutide antibody status. Subjects will be defined as positive or negative for anti-albiglutide antibody status. Anti-albiglutide positive subjects are defined as subjects with an anti-albiglutide antibody result of positive at any visit (including those with a positive

result at baseline, regardless of whether they had a post-baseline positive result). Anti-albiglutide negative subjects are defined as those subjects with an anti-albiglutide antibody result of negative at all visits.

8.2.1.7.9. Systemic Allergic Reactions

Potential systemic allergic reactions are reported by the investigators on the hypersensitivity eCRF.

For subjects with an investigator reported systemic allergic reaction, hypersensitivity medical history will be listed, along with additional hypersensitivity data collected following a systemic allergic reaction.

8.2.1.7.10. Liver Events

By-subject listings of all the data elements collected on the eCRF liver event pages will be presented for subjects who experience adverse liver events, as defined per protocol. This includes data recorded in the following eCRF forms: liver monitoring/stopping event recorded; liver events; alcohol intake at onset of liver event; medical conditions at onset of liver event; liver biopsy; liver imaging; and liver PK.

A summary table of Liver Monitoring/Stopping Event Reporting will also be presented using data from the liver events eCRF. This summary table will include events in both the on-therapy and post-therapy phases.

Additionally, a table summarising liver events identified by a Customised MedDRA Query (CMQ) will be presented for the on-therapy phase.

See Section 8.2.2 for additional related summaries based on laboratory data.

8.2.1.7.11. Renal Impairment

Renal impairment is reported by the investigators on the renal impairment eCRFs. By-subject listings of all the data elements collected on the eCRF renal impairment pages will be presented for subjects who experience renal impairment. This includes data recorded in the following eCRF forms: renal impairment; spot urine sample; timed urine sample; and additional information.

8.2.1.7.12. Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) events will be identified by a Customized MedDRA Query (CMQ).

8.2.1.7.13. Appendicitis

Appendicitis events will be identified by a Customized MedDRA Query (CMQ).

8.2.1.7.14. Pancreatic Cancer

Pancreatic cancer events will be identified by a Customized MedDRA Query (CMQ).

8.2.1.7.15. Malignant Neoplasms

Malignant neoplasms will be identified by a Standard MedDRA Query (SMQ).

8.2.2. Overview of Planned Clinical Laboratory Analyses

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

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 7 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Changes from Baseline				Y		
Chemistry Results by PCI Criteria	Y					
Hematology						
Hematology Changes from Baseline				Y		
Hematology Results by PCI Criteria	Y					
Urinalysis						
Urine Concentration Changes from Baseline				Y		
Summary of Urinalysis Dipstick Results	Y					
Hepatobiliary (Liver)						
Hepatobiliary Laboratory Abnormalities	Y					
Subjects Meeting Hepatobiliary Laboratory Criteria			Y			
Scatter Plot of Maximum vs. Baseline for ALT		Y				
Scatter Plot of Maximum Total Bilirubin vs Maximum ALT		Y				
All Laboratory						
All Laboratory Data for Subjects with any Value of PCI			Y			
Laboratory Data with Character Results			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.2.1. Chemistry, Hematology and Urinalysis

Established or generally acknowledged methods, normal ranges, and quality control procedures will be supplied by Q2 Solutions for the study records.

Only data from the central laboratory will be included in the tables, figures and listings. Data from local laboratories will not be included.

Glucose data from the eDiary card will not be included in any laboratory TFLs.

The number of subjects with results relative to the potential clinical importance criteria will be summarised by laboratory test and category (including liver function tests). Data will be summarised by visit, including 'any on-therapy visit' and 'any post-baseline visit'. The criteria for laboratory values of potential clinical importance are detailed in Section 11.7.1.

Urinalysis data with categorical results will be summarised at each assessed timepoint by treatment group, using number and percentage of subjects with each category.

8.2.2.2. Hepatotoxicity

In addition, a more detailed summary of hepatobiliary laboratory abnormalities will be provided for liver function tests, including ALT, ALP and total bilirubin. A listing of which subjects met each Hepatobiliary laboratory criteria post-baseline will also be produced.

A graphical presentation of maximum ALT (x ULN) versus baseline ALT (x ULN) value for each subject on treatment will be produced.

A graphical presentation of maximum total Bilirubin (x ULN) versus maximum ALT (x ULN) values on treatment will be produced.

8.2.3. Overview of Planned Other Safety Analyses

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

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 8 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y					
Change from Baseline in ECG Values by Visit				Y		
ECG Results by PCI Criteria	Y					
QTcF and QTcB Values by Visit and Category	Y					
Change from Baseline in QTcF and QTcB Values by Visit and Category				Y		
Abnormal ECG Findings			Y			
All ECG Data for subjects with any value of PCI			Y			
Vital Signs						
Change from Baseline in Vital Signs by Visit				Y		
Vital Signs Results by PCI Criteria	Y					
All Vital Signs for subjects with any value of PCI			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.3.1. Vital Signs

The vital signs summary will be based on recordings of systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm). Note: weight is assessed as part of efficacy.

The number of subjects with vital sign results relative to the potential clinical importance criteria will be summarised by test and category. Data will be summarised by visit, including 'any on-therapy visit' and 'any post-baseline visit'. The criteria for vital signs of potential clinical importance are detailed in Section 11.7.3.

8.2.3.2. Electrocardiograms

ECG parameters will be collected in triplicate at each time point including heart rate, QRS interval, QT interval, QT interval – Bazett correction (QTcB), QT interval – Fredericia correction (QTcF), RR interval and PR interval. The mean of the triplicate measurements will be calculated for each ECG parameters and used in any derivation of summary statistics. For ECG findings and PCI criteria, all three ECGs will be considered and the worst case result will be summarised. The baseline value used for assessing PCI will be the mean of the triplicate measurements.

The number of subjects with ECG values of potential clinical importance will also be summarised. Data will be summarised by visit, including 'any on-therapy visit' and 'any post-baseline visit'. The criteria for ECG values of potential clinical importance are detailed in Section 11.7.2. A summary of the number and percentage of subjects in overall ECG interpretation and abnormal findings will be displayed by treatment group over time.

Additionally, categorical summaries for QTcB and QTcF values (<450 msec, ≥450 to 480 msec, ≥480 to <500 msec, and ≥500 msec) and QTcB and QTcF change from baseline values (0 to <30 msec, ≥30 to <60 msec, and ≥60 msec) will be presented by treatment group. The mean of the triplicate measurements will be used as the parameter in this summary table.

In this study, a larger proportion of QTc results were reported with an 'other' method of correction (rather than QTcB or QTcF). This will be handled as follows. For summaries of PCI, this will be assessed for QTc using QTcF values. In cases where QTcF is not reported and is unable to be derived, then PCI will be assessment using the value of QTc (other method of correction). Data will be presented separately for the two QT correction methods. For other summary tables (change from baseline in QTc and categories of QTc), data will be presented separately for QTc (other method of correction).

8.3. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" population, unless otherwise specified.

Albiglutide plasma concentration data will be summarised for the albiglutide group. Descriptive summary statistics will be presented for each nominal scheduled visit where samples were collected (Week 4, Week 6, Week 8 and Week 16).

Mean (sd) plasma concentration versus scheduled time profiles and median plasma concentration versus scheduled time profiles will be presented in separate figures on both linear and semi-logarithmic scales.

A scatter plot of individual plasma concentrations versus scheduled time will be produced. In addition to individual plasma concentrations, this will also show a box and whisker plot of median and appropriate percentiles.

There will be no statistical analysis of PK parameters.

Table 9 provides an overview of the planned analyses, with full details being presented in Appendix 13: List of Data Displays.

Table 9 Overview of Planned Pharmacokinetic Analyses

Parameter	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Albiglutide plasma concentration	Y	Y[1]		Y				

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Mean (Linear and Semi-Log on same display) and Median (Linear and Semi-Log on same display) plots will be created. A box and whisker/scatter plot will also be produced.

8.3.2. Pharmacokinetic Parameters

8.3.2.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Win Nonlin.
- The population pharmacokinetic parameters will be calculated by pop PK modelling in NONMEM.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 10 will be determined from the albiglutide plasma concentration-time data, as data permits.
- All PK parameters described in Table 10 will be derived and reported by the GSK CPMS group.

Table 10 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC (0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t))
AUC (0-t)/t	Average concentration over the time period
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Pop.CL/F	Population apparent clearance
Pop.V/F	Population apparent volume of distribution
Pop.Ka	Population first-order absorption rate constant

NOTES:

- Additional parameters may be included as required.

8.3.3. Population Pharmacokinetic (PopPK) Analyses

- The primary goal of this analysis is to characterize the population pharmacokinetics of albiglutide administered subcutaneously in subjects with NOT1DM.
  - The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of albiglutide in this population will be investigated.
- A summary of the planned population pharmacokinetic analyses are outlined below:
  - Drug plasma concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM.
  - Individual post-hoc estimated PK parameters will be summarised descriptively.
  - To support this analysis a NONMEM file will be generated.
  - The details for the dataset specifications are provided in Appendix 10: Population Pharmacokinetic Analyses with detailed methodology for the analysis.

The population PK parameters (e.g., CL/F, V/F, and Ka) will be summarised for the albiglutide group. The relationship between albiglutide PK parameters and subject covariates of interest will be evaluated in the population PK model. All population PK analyses will be performed and reported by the GSK CPMS group.

8.4. Pharmacokinetic / Pharmacodynamic Analyses

In a change to the planned analysis specified in the protocol, exploratory endpoints will not be summarised or presented graphically. Therefore, PK/PD analyses specified under the exploratory objectives section of the protocol will not be performed. There will be no data listing for this exploratory endpoint.

In a change to the planned analysis specified in the protocol, analysis of the secondary endpoint of 'population estimates of PD parameters (e.g., Emax, EC_{50}), associated inter-subject variability and residual error if permitted by the data' will not be conducted.

9. OTHER STATISTICAL ANALYSES

9.1. Overview of Planned Exploratory Efficacy Analyses

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

Table 11 provides an overview of the planned exploratory analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 11 Overview of Planned Exploratory Efficacy Analyses

Endpoint / Parameter/ Display Type	Absolute				Change from BL			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Correlation between 120 minutes urinary C-peptide creatinine ratio and MMTT C-peptide AUC								
Listing of 120 minutes urinary C-peptide creatinine ratio				Y[1]				Y[1]
T1DM-associated auto-antibodies (anti-GAD, anti-IA-2, IAA)								
Listing of ant-GAD, anti-IA-2 and IAA results				Y[1]				Y[1]
ADDQoL								
Listing of ADDQoL data				Y[1]				
β-cell function / Insulin secretion parameter								
No analyses will be performed.								
PBMC and Serum sample for Exploratory Biomarker Analysis								
No TFLs currently planned. A decision on whether to analyse biomarker samples will be made after review of efficacy endpoints at the end of the study								

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Single listing contains absolute and change from baseline values

In a change to the planned analysis specified in the protocol, exploratory endpoints will not be summarised or presented graphically. Data will be listed only.

Anti-GAD data: Due to changes in the test kit used to analyse results, the numeric anti-GAD titre results cannot be combined for the two different test kits used. The data listing will identify those analysed using the RIA test kit and those analysed using the ELISA test kit. This is likely to result in missing data as for some subjects the test kit changed after the baseline sample was analysed.

ADDQoL: Data listings will present the two overview items, and the individual 19 domains (impact rating and importance rating presented for each individual domain). Weighted impact scores will not be derived or presented.

β-cell function, expressed as an insulin secretion parameter, will not be explored by the GSK CPMS group, therefore there will be no data listing for this endpoint.

PBMC and serum samples for exploratory biomarker analysis will be collected at various timepoints throughout the study. A decision on whether to analyse biomarker samples will be made after review of efficacy endpoints at the end of the study. Exploratory biomarkers may include CD8-positive antigen-specific T-cells and biomarkers for β-cell death. Any analyses will be reported separately to the CSR and will not be included as part of the SAC delivery.

9.2. Immunogenicity Analyses

Anti-albiglutide antibody results will be presented by treatment group for the safety population. Data will be presented:

- By visit (including 'any visit' and 'any post-baseline visit' categories)
- By therapy phase (pre-therapy, on-therapy and post-therapy)
- By visit (including 'any visit' and 'any post-baseline visit' categories), excluding subjects with positive anti-albiglutide antibody at Baseline

Each summary table will present the number and percentage of subjects with positive results (anti-albiglutide antibody, anti-GLP-1 antibody, anti-HA(albumin) antibody, and anti-albiglutide neutralising antibody) at each assessment. Results will be presented:

- Where the denominator is the number of subjects who had at least one non-missing anti-albiglutide antibody result during that particular visit/therapy phase.
- Where the denominator is the number of subjects with positive anti-albiglutide antibody results at that assessment.

In addition, summary statistics for the anti-albiglutide antibody titre will be presented.

All immunogenicity data including antibody titres will be listed.

Characteristics of injection site reactions will be presented by anti-albiglutide antibody status (positive/negative) as described in Section 8.2.1.7.8.

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11. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.1	Appendix 1: Time and Events
Section 11.2	Appendix 2: Assessment Windows
Section 11.3	Appendix 3: Treatment States & Phases
Section 11.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.7	Appendix 7: Values of Potential Clinical Importance
Section 11.8	Appendix 8: Examination of Covariates and Subgroups
Section 11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Section 11.10	Appendix 10: Population Pharmacokinetic Analyses
Section 11.11	Appendix 11: Mixed Meal Tolerance Test (MMTT) – Supplementary Information
Other RAP Appendices	
Section 11.12	Appendix 12: Abbreviations & Trade Marks
Section 11.13	Appendix 13: List of Data Displays
Section 11.14	Appendix 14: Example Mock Shells for Data Displays

11.1. Appendix 1: Time & Events

11.1.1. Protocol Defined Time & Events

Study Procedure	Visit	Screening		Treatment To include at least weekly telephone contact (where there is no study visit) from Baseline to Week 16[2]									Off treatment follow-up	Early Withdraw [27]
				Baseline										
	Visit	1	2[3]	3	4	5	6	7	8	9	10	11	12	
	Week[1]	-8 to 0		0	2	4	6	8	16	28	40	52	64	
Written informed consent		x												
Demography and history (medical, disease, therapy)		x												
Review eligibility criteria		x	x	x										
Provide diet, exercise and home glucose monitoring advice			x	x	x	x	x	x	x	x	x	x		
Efficacy assessments														
Mixed meal tolerance test[4]			x						x	x		x	x	
7 point glucose profile[5]				x						x		x		
72 hour continuous glucose monitoring [6]				x						x		x		
Review glucose monitoring/insulin dose with subject			x	x	x	x	x	x	x	x	x	x	x	
ADDQoL				x								x		
Safety assessments														
Concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[7]		x		x					x	x	x	x	x	x
Vital sign[8]		x		x	x	x	x	x	x	x	x	x	x	x
12-lead ECG[9]				x		x			x	x	x	x	x	
Adverse events		X[10]	X[10]	x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycaemic events[11]			x	x	x	x	x	x	x	x	x	x	x	x
Laboratory assessments														
HbA_{1c}				x		x		x	x	x	x	x	x	x
Triglycerides (fasting)[12]		x												
T1DM associated auto-antibody titres[13]		x[14]				x			x	x	x	x	x	

Study Procedure	Visit	Screening		Treatment To include at least weekly telephone contact (where there is no study visit) from Baseline to Week 16[2]									Off treatment follow-up	Early Withdraw [27]
				Baseline										
	Visit	1	2[3]	3	4	5	6	7	8	9	10	11	12	
	Week[1]	-8 to 0		0	2	4	6	8	16	28	40	52	64	
Immunogenicity [15]				x	x	x	x	x	x	x	x	x	x	
Haematology[16]/chemistry[17]		x		x	x	x		x	x	x	x	x	x[18]	x
Urinalysis[19]		x		x		x		x	x	x	x	x	x[18]	x
Pharmacogenetics[20]				x										
Pharmacokinetic sample[21]						x	x	x	x					
PBMC Biomarker sample [22]				x		x			x	x	x	x	x	
Serum Biomarker sample [23]				x		x			x	x	x	x	x	
Pregnancy test[24]		U		U		U		U	U	U	U	U	U	U
HbsAg, and hepatitis C antibody[25]		x												
Dispense Investigational product (IP)				x		x	x	x	x	x	x			
IP compliance					x	x	x	x	x	x	x	x		x
Register visit into IVRS[26]		x	x	x	x	x	x	x	x	x	x	x	x	x

NOTES :

- ADDQoL = audit of diabetes dependent quality of life; ECG = electrocardiogram; HbA1c = glycosylated haemoglobin, HbsAg =-hepatitis B surface antigen ;IVRS = interactive voice response system, PGx = pharmacogenetics; S = serum; U = urine, PBMC = peripheral blood mononuclear cells; T1DM = type 1 diabetes mellitus
- [1] Study visits from Baseline through to Week 8 will have a visit window of ±3 days. Study visits from Week 16 through to Week 64 will have a visit window of ±7 days. Subjects will not be considered out of compliance if visit windows extend because of events (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation will be at the discretion of the medical monitor.
- [2] Telephone call to occur between study visits at least weekly from Baseline to Week 16 (it is recommended that calls occur every 3-5 days during the first 2 weeks of randomised treatment and after Week 6 when the study drug dose is increased), and at Week 22, Week 34, Week 46 and as required to advise subjects on insulin dose adjustments, adverse event (AE) monitoring, hypoglycaemia monitoring, and concomitant medication usage.
- [3] Visit to be performed once other screening tests indicate eligibility.
- [4] See Protocol Section 6.3.2.1/ Section 11.11 for details on the MMTT. Screening MMTT to be performed once other screening test indicate eligibility and at least 28 days from the date of diagnosis of T1DM. Take a urine sample at 120 mins post- MMTT for assessment of urinary C-peptide and urinary creatinine. Subjects to void their bladders just prior to the start of the MMTT.
- [5] 7 point glucose self-monitoring: before and 2 hours after breakfast, lunch and dinner, at bedtime, on one day in the week prior to each scheduled assessment (to coincide with one of the days that the CGM is conducted).
- [6] To be performed in the week prior to the visit. Subject to make an additional visit to the study site to have the CGM monitor fitted/inserted
- [7] Perform complete physical examination at Screening and Week 52. Perform brief physical examination at other time points.
- [8] Vital signs include weight, blood pressure, and heart rate (pulse). Height to be measured at Screening only. Calculate body mass index at Screening.

- [9] All 12-lead ECGs to be performed in triplicate (approx 10 mins apart) and before measurement of vital signs and collection of blood samples for laboratory testing. Subjects to be semi-recumbent for 10 to 15 minutes before ECGs.
- [10] Only diabetic ketoacidosis SAEs, hypoglycaemia SAEs and SAEs thought to be related to study procedures need to be reported during Screening
- [11] See protocol Section 6.4.2 for hypoglycaemia event criteria and reporting requirements. . Urine ketostix to be performed regularly according to clinical practice (see protocol Section 5.1.2)
- [12] Fasting is defined as no food or drink (except water) for at least 8 hours before blood draw.
- [13] Anti-GAD, anti-IA2, IAA
- [14] If results are required quickly for eligibility purposes, local labs may be used for the Screening sample only. If local labs are used, a screening sample must also be sent to the central lab.
- [15] Immunogenicity sampling is to be done prior to dosing throughout study
- [16] Haematology to include complete blood count with haemoglobin, other red blood cell indices, white blood cell count differential, and platelet count.
- [17] Clinical chemistry to include: glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, uric acid, magnesium, phosphorus.
- [18] If abnormal at Week 52
- [19] Urinalysis to include: specific gravity, pH, glucose, protein, blood by dipstick (if warranted, a microscopic evaluation will be completed).
- [20] Blood sample for pharmacogenetics (PGx) can be collected at any time during the study after the PGx informed consent has been obtained and the subject has been randomly assigned to a treatment group.
- [21] 2ml blood sample. Sample at Week 4 and Week 6 to be taken at least 2 days (48 hours) after the most recent dose of study medication and at any time prior to the next scheduled dose. At Week 6 or any subsequent visit where up or down titration of albiglutide/matching albiglutide placebo coincides with PK sampling, the PK sample must be taken prior to titration, such that it is taken no more than 16 hours prior to the subsequent dose. At Week 8 and Week 16, sample to be collected at least 2 days (48 hours) after a dose but not within 4 days of another sample.
- [22] 8ml blood sample to achieve approx 4 million viable PBMC sample – split into 2 samples
- [23] 5ml blood sample to achieve approximately 2 ml serum sample – split into 3 samples
- [24] Pregnancy test for women of child-bearing potential only and at any other time that pregnancy is suspected (U = urine).
- [25] If hepatitis C antibody positive, RNA polymerase chain reaction should be performed on the same sample to confirm the result.
- [26] Randomisation to occur at baseline visit.
- [27] If a subject discontinues study medication, they will be asked to continue to participate in the study and continue to attend study visits where a MMTT is performed. During these visits, as well as a MMTT, HbA1c, weight, AEs, hypoglycaemia and insulin usage should be assessed. Subjects should also continue to complete their diary and must adhere to the insulin titration algorithm/guidelines as defined in the protocol through to Week 64. If the subject refuses to continue attending these visits after stopping study medication, complete this early withdrawal visit.

11.2. Appendix 2: Assessment Windows

11.2.1. Protocol Defined Visit Windows for Scheduled Visits

For HbA1c, where unscheduled visits will be used if scheduled assessments are missing and the unscheduled assessments fall in the protocol defined time period for the missing scheduled visit (see Section 11.4.3). The early withdrawal visit will be handled in the same way as unscheduled visits. The protocol defined time period for the visits is as specified below:

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
HbA1c	HbA1c	Day 1 [1]	Day -3	Day 1 [1]	Baseline (Week 0)
		Day 28	Day 25	Day 31	Week 4
		Day 56	Day 53	Day 59	Week 8
		Day 112	Day 105	Day 119	Week 16
		Day 196	Day 189	Day 203	Week 28
		Day 280	Day 273	Day 287	Week 40
		Day 364	Day 357	Day 371	Week 52
		Day 448	Day 441	Day 455	Week 64

NOTES :

- [1] Pre-dose assessment on Day 1

11.2.2. Assigning Visits to Insulin Use Data

Subjects will record their daily insulin use in an electronic diary. This information will be transferred to the concomitant medications dataset. However, study visit is not captured in the concomitant medications dataset, therefore insulin data will need to be assigned to the relevant study visit.

Only data at Baseline, Week 4, 8, 16, 28, 40, 52 and 64 will be included in summary tables and analyses. Data from all time points will be listed.

Only data from the 3 days immediately preceding the study visit will be used in calculation of mean daily insulin, even if more than 3 days of data are recorded.

Study visit will be assigned as follows:

A visit date will be used for each of the time-points (Baseline, Week 4, 8, 16, 28, 40, 52 and 64). If the date of insulin is in the 3 days immediately preceding the study visit then this will be assigned to the appropriate study visit.

e.g.

- Week 52 visit date = 15-MAY-2016
- Insulin use on 14-MAY-2016, 13-MAY-2016 and 12-MAY-2016 will be assigned as Week 52.

11.3. Appendix 3: Treatment States and Phases

11.3.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment, unless otherwise specified.

Treatment Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Dates

11.3.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

11.3.2.1. Treatment States for AE Data

Treatment State	Definition
Pre-Therapy	The onset date of the AE is before the treatment start date. AE Start Date < Study Treatment Start Date
On-Therapy	If AE onset date is on or after treatment start date & on or before treatment stop date + 56 days. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 56 days
Post-Therapy	If AE onset date is after the treatment stop date + 56 days. AE Start Date > Study Treatment Stop Date + 56 days
Onset Time Since 1st 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.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	The relationship question on the CRF 'Is there a reasonable possibility that the AE may have been caused by the Study Treatment?'. The investigator additionally specifies if this is in relation to blinded study medication (albiglutide/placebo) or Insulin. The AE will be considered to be drug-related if the relationship is marked 'YES' and it is marked as related to blinded study medication (albiglutide/placebo). If the AE is marked as related to insulin only it will not be included as drug-related. If a relationship to the study drug is missing or unknown, after the start of treatment, it will be assumed for the purpose of analyses to be drug-related.

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Therapy.

11.3.2.2. Treatment States for Subject-Reported Hypoglycaemic Events, Medication and Non-Drug Therapy Data

Treatment states for subject-reported hypoglycaemic events, medications and non-drug therapy data are assigned according to the same rules as AE data.

Treatment State	Definition
Pre-Therapy	The onset date of the event/medication is before the treatment start date. Event/Medication Start Date < Study Treatment Start Date
On-Therapy	If event/medication onset date is on or after treatment start date & on or before treatment stop date + 56 days. Study Treatment Start Date ≤ Event/Medication Start Date ≤ Study Treatment Stop Date + 56 days
Post-Therapy	If event/medication onset date is after the treatment stop date + 56 days. Event/Medication Start Date > Study Treatment Stop Date + 56 days

NOTES:

- If the study treatment stop date is missing then the assessment will be considered to be On-Therapy

11.3.2.3. Treatment States for Immunogenicity and Other Safety Data

For immunogenicity data and other safety parameters that are assessed prior to administration of study medication on dosing days, the therapy periods will be defined as:

Treatment State	Definition
Pre-Therapy	The assessment date is on or before the treatment start date. Date ≤ Study Treatment Start Date
On-Therapy	The assessment date is after treatment start date & on or before treatment stop date + 56 days. Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 56 days
Post-Therapy	The assessment date is after the treatment stop date + 56 days. Date > Study Treatment Stop Date + 56 days

NOTES:

- If the study treatment stop date is missing then the assessment will be considered to be On-Therapy

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
PPD IVRS		Data Displays for Reporting	
Code	Description	Description	Order [1]
1	Albiglutide 30 mg (with treatment-masked increase to 50 mg weekly at Week 6)	Albiglutide	2
2	Albiglutide-matching Placebo	Placebo	1

NOTES:

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

11.4.2. Baseline Definition & Derivations

11.4.2.1. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-dose assessment. That is, the baseline value for an assessment is defined as the last non-missing value with an assessment date on or before the date of the first dose of study treatment.

Generally time of assessment is not collected; hence this definition assumes that assessments collected on the same day as treatment start were done prior to treatment start. The following table shows the assessments which can be considered to be baseline assessments.

Data will be presented in summary tables as 'Baseline' regardless of which visit it is derived from.

Parameter	Study Assessments Collected Before Study Treatment (can be considered as baseline)		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Safety			
Vital Signs	X	X	Latest pre-dose
12 Lead ECG		X	Latest pre-dose
BMI	X		Latest pre-dose
Laboratory	X	X	Latest pre-dose
Immunogenicity Sample		X	Latest pre-dose

Parameter	Study Assessments Collected Before Study Treatment (can be considered as baseline)		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Efficacy			
Mixed Meal Tolerance Test (MMTT)	X		Latest pre-dose
Blood Sample for HbA1c		X	Latest pre-dose
PD/Biomarkers			
PBMC Biomarkers		X	Latest pre-dose
Serum Biomarkers		X	Latest pre-dose

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

11.4.2.2. 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]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.4.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

11.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
SAC outputs and datasets will be created at PPD. The final outputs and datasets will be imported into HARP	
HARP Server	: us1salx00259
HARP Area	: /arenv/arprod/gsk716155/glp110933/final/
QC Spreadsheet	: /arenv/arprod/gsk716155/glp110933/final/documents

Reporting Process
Analysis Datasets
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.0, define.xml V2, Pinnacle V2.2.0). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will be generated for final statistical analysis complete (SAC).

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Nominal scheduled visit will be used unless otherwise specified. • 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 Statistical Principle 5.05.1). • All data (including unscheduled or unplanned readings) will be presented within the subject's listings.

Reporting Standards	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables, with the exception of: o HbA1c, where unscheduled visits will be used if scheduled assessments are missing and the unscheduled assessments fall in the protocol defined time period for the missing scheduled visit (see Section 11.2). The early withdrawal visit will be handled in the same way as unscheduled visits. o Unscheduled visits will be included in laboratory, vital signs and ECG summaries which look at worst-case or maximum values of potential clinical importance or QTC categories. • Unscheduled visits will not be included in figures, except as detailed above (including hepatobiliary 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, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) – 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	N, n, mean, standard deviation (SD), minimum, median, maximum
Summary Tables	Plasma concentration data will be summarised. All other PK and population PK parameters will be derived and reported by the GSK CPMS group.
Listings	Plasma concentration data will be listed.
Graphical Displays	
• Refer to IDSL Statistical Principals 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. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. Generally, nominal visit is used in this study and this rule would not apply then. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from the date of first dose of study treatment:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Date of First Dose → Study Day = Ref Date –Date of First Dose
  • Ref Data ≥ Date of First Dose → Study Day = Ref Date – (Date of First Dose) + 1
 	
Note: Date of first dose is Day 1 and the day before the date of first dose is Day -1 (there is no Day 0).

11.5.2. Study Population

Demographics and Baseline Characteristics
Age
• Only birth year is collected in the eCRF; birth day and month will be imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Age, in whole years, will be calculated with respect to the date of randomisation using the imputed date of birth • For subjects not randomised, age, in whole years, will be calculated with respect to the baseline visit date if visit done and date is available, and with respect to screening visit date otherwise.
Age Ranges
• The demographic summary table will include the standard age ranges: ≤18 years, 19 to 64 years, ≥65 years. • The summary of age ranges table will include only the Adult (18 to 64 years) category • These are standard categories and cannot be changed, even though the study age range is 18 to 30 years (inclusion criteria).
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**

Demographics and Baseline Characteristics

Race

- The five high level FDA race categories and two designated Asian subcategories are:

1) American Indian or Alaska Native
2) Asian
   a) Central/South Asian Heritage
   b) Japanese Heritage/East Asian Heritage/South East Asian Heritage
3) African American/African Heritage
4) Native Hawaiian or Other Pacific Islander
5) White

- Note: subjects may report more than one race category in the CRF. This will be handled as follows in summary tables. A subject will only be represented in a single category. A subject who selects a combination of races will be counted as either "MIXED ASIAN RACE", "MIXED WHITE RACE" or "MULTIPLE" (depending on the race categories selected) but not in each of the constituent terms. Therefore the counts will add up to the total number of subjects with a response, and the percentages will add to 100%.

Baseline HbA1c

- Baseline HbA1c categories are (%): ≤6.5%, >6.5 to 7.0%, >7.0 to 8.0%, >8.0 to 9.0%, >9.0%

Time from Diagnosis to First Dose of Study Treatment

- The time from diagnosis to first dose of study drug is calculated as the days lapsed between date of first dose and Type 1 diabetes diagnosis date:

  Date of first dose – Diagnosis date

- Time from diagnosis categories will be (days): 28-42; 43-56; >56.

Presence of T1DM associated antibodies

- The following antibodies are assessed at baseline and at Week 4, Week 16, Week 28, Week 40, Week 52 and Week 64: antibody to glutamic acid decarboxylase (anti-GAD); antibody to protein tyrosine phosphatase-like protein (anti-IA-2); and insulin autoantibody (IAA). Only baseline data will be summarised.
- For each antibody the baseline data will be classed as positive or negative. Numeric results will be available from the central laboratory dataset. These numeric results will be translated into the positive/negative classification based on the Normal Range High value provided for each test (LBORNRHI):
  - <Normal Range High value: Negative
  - ≥Normal Range High value: Positive
- Note, for anti-GAD the test was performed using two different test kits 1) old RIA test kit (units KU/L) and 2) new ELISA test kit (units IU/ML). And therefore has different Normal Range High values depending on which test kit was used.
- Summaries of T1DM associated antibodies (anti-GAD, anti-IA-2, IAA) will only include data from the central laboratory

Demographics and Baseline Characteristics

Number of Positive Type 1 Associated Antibodies: Anti-GAD/Anti-IA-2/IAA and Anti-GAD/Anti-IA-2 (excluding IAA)

- The number of positive type 1 associated antibodies will be calculated for each subject using all three antibodies: anti-GAD, anti-IA-2 and IAA. Categories will be 1, 2 or 3.
- The number of positive type 1 associated antibodies will also be calculated for each subject using two of the three antibodies: anti-GAD and anti-IA-2. IAA will not be included. Categories will be 1 or 2.

DEFEND-1 Demographic and Baseline Characteristics

- Age at screening will be used from the DEFEND-1 datasets.
- BMI will be used from the DEFEND-1 datasets.
- Time from diagnosis to first dose of study drug will be calculated as described above.
- Baseline HbA1c will be categorized as described above
- The presence of type 1 associated antibodies will be reported for anti-GAD and anti-IA-2 (positive/negative)
- The number of positive type 1 associated antibodies will be reported using anti-GAD and anti-IA-2 results (categories 0/1/2)

Extent of Exposure

Duration of Exposure (including breaks)

- 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
- Subjects who were randomised but did not report a treatment start date will be categorised as having zero days of exposure.
- Duration of exposure categories will be: ≤8 weeks; >8 weeks to ≤12 weeks; >12 weeks to ≤24 weeks; >24 weeks to ≤40 weeks; >40 weeks to ≤52 weeks; >52 weeks.
- Subjects will be assigned to categories using exposure calculated in days:
  - ≤ 8 weeks: ≤56 days
  - >8 weeks to ≤12 weeks: >56 days to ≤84 days
  - >12 weeks to ≤24 weeks: >84 days to ≤168 days
  - >24 weeks to ≤40 weeks: >168 days to ≤280 days
  - >40 weeks to ≤52 weeks: >280 days to ≤364 days
  - >52 weeks >364 days
- Total person time on treatment (years) will be calculated using:
  Total person time on treatment=([Treatment Stop Date – Treatment Start Date+1] + 56)/365.25
- Note: safety data for events that occurred up to 56 days after the last dose of study medication are included as 'on-therapy' – this period was chosen in consideration of the long half-life of albiglutide.

Duration of Exposure (excluding breaks)

- Duration of exposure excluding breaks will be calculated as:
  (Treatment Stop Date – Treatment Start Date +1) – (7 * number of missed doses).
- Duration of exposure categories will be assigned as defined above.
- Total person time on treatment (years) excluding breaks will not be derived or presented.

Extent of Exposure

Duration of Exposure by Actual Dose Level

- The albiglutide dose in this study will start at 30-mg weekly and be increased to 50-mg weekly at Week 6 if the patient is able to tolerate the 30 mg weekly dose. Subjects experiencing GI intolerability on the 50 mg dose may decrease back to the 30 mg dose following discussion between the investigator and the medical monitor.
- For albiglutide subjects, the duration of exposure by actual dose level will be calculated as the number of days on 30mg study treatment and the number of days on 50mg study treatment as follows:
- For subjects who do not up-titrate:
  Duration of exposure to 30mg = duration of exposure (days)
  Duration of exposure to 50mg = 0

- For subjects who up-titrate, with no subsequent down-titration:
  Date of up-titration = date of first dose of 50mg IP
  Duration of exposure to 30mg = (date of up-titration-1) – date of first dose 30mg IP + 1
  Duration of exposure to 50mg = date of last dose IP (50mg) – date of first dose 50mg IP +1

- For subjects who up-titrate, but subsequently down-titration back to 30mg:
  Date of up-titration = date of first dose of 50mg IP
  Date of down-titration = date of first dose 30mg IP after 50mg IP
  Duration of exposure to 30mg (1) = (date of up-titration-1) – date of first dose 30mg IP + 1
  Duration of exposure to 30mg (2) = date of last dose IP (30mg) – date of down-titration +1
  Duration of exposure to 30 mg = Duration of exposure to 30 mg (1) + (2)
  Duration of exposure to 50mg = (date of down-titration-1) – date of up-titration + 1

- Note: for all patients the total duration of exposure should equal duration of exposure to 30mg + duration of exposure to 50mg.
- Note: similar rules will be applied for any subjects who do not follow the standard titration plan.
- For placebo patients, the duration of exposure by actual dose level will not be calculated.
- Categories for duration of exposure by actual dose level will be as described for total duration of exposure.
- Total person time on treatment (years) will be calculated for each actual dose level as:
  For each albiglutide subject, for the last actual dose level received the duration of exposure to 30mg/50mg (days) will have 56 days added. The duration of exposure to 30mg/50mg (days) will then be summed across subjects and converted into years by dividing by 365.25.

Extent of Exposure
Compliance
• Treatment compliance will be calculated for each subject as the total number of doses actually taken (numerator) divided by the number of doses that should have been taken (denominator), multiplied by 100. Compliance will be calculated based on information recorded on the study treatment eCRF (using date of first dose, date of last dose and missed dose information to determine compliance) ○ Numerator = ceiling[(date of last dose – date of first dose +1)/7] – number of missed weekly doses ○ Denominator = ceiling[(date of last dose – date of first dose +1)/7] Where ceiling [x] = smallest integer ≥x Note: numerator/denominator are in terms of weeks of treatment • Categories of treatment compliance will be created as follows: missing, <80%, ≥80%

11.5.3. Safety

ECG Parameters
ECG parameters will be collected in triplicate at each time point. The mean of the triplicate measurements will be calculated for each ECG parameter and used as the value for that time-point. For ECG findings and PCI criteria, all three ECGs will be considered and the worst case result will be summarised. For PCI criteria comparing to baseline, the mean of the triplicate measurements at baseline will be used as the baseline value.
ECG Findings
For the summary of ECG findings (where assessed in triplicate at each time-point) a 'worst case' assessment for each subject will be derived, so that the number of subjects and percentages sum to 100% within each time-point. For ECG findings, the ordering of the worst case approach will be • For baseline assessments, the ordering (from worst) will be abnormal clinically significant, abnormal not clinically significant, then normal. • For post-baseline assessments, the ordering (from worst) will be any clinically significant change unfavourable, any clinically significant change favourable, then 'no change or insignificant change'.
RR Interval
• RR is not collected for machine read ECG. • 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: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

ECG Parameters

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive the RR interval if it is available (i.e., collected on the eCRF). If the RR interval is not available then it may be derived using the formula above.

Corrected QT Intervals

- Where QTcB and/or QTcF are reported in the eCRF then these reported values should be used (with no re-derivation).
- 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 or derived then missing QTcB and/or QTcF will be derived as:

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

- If only QTc (other method of correction) is reported then QTcB and QTcF are unable to be derived. Then data for QTc (other method of correction) will be summarised. This will be presented as a separate parameter.

QTcF / QTcB Categories

- QTcB and QTcF values will be summarised using the following categories:
- Absolute: <450 msec; ≥450 to 480 msec; ≥480 to <500 msec; and ≥500 msec
- Change from baseline: 0 to <30 msec; ≥30 to <60 msec, and ≥60 msec.
- The mean of the triplicate measurements at each visit will be used in these summaries.
- Data for QTc (other method of correction) will also be presented as a separate parameter in these summary tables.

Adverse Events

AE Density

- AE density, also referred to as event density, will be calculated as the number of events in a given period divided by the total person time on treatment (in years) of subjects at risk at the beginning of the same period. All AE densities will be presented per 100 person-years (by multiplying the above defined statistics by 100). i.e.:
- On-therapy AE density = 100 x number of on-therapy AEs/total person time on treatment (years)
- Note: see exposure derivations for total person time on treatment calculation.

AE's of Special Interest
• **Cardiovascular Events – investigator reported**: defined as events reported by the investigator on the specific AESI eCRFs (congestive heart failure CRF; cerebrovascular events/stroke and transient ischemic attack CRF; deep vein thrombosis/pulmonary embolism CRF; myocardial infarction / unstable angina CRF; peripheral arterial thromboembolism CRF; pulmonary hypertension CRF; revascularisation CRF; valvulopathy CRF; and arrhythmias CRF) • **Atrial Fibrillation / Atrial Flutter – investigator reported**: defined as events reported by the investigator on the specific atrial fibrillation/atrial flutter eCRF. • **Pneumonia – investigator reported**: defined as events reported by the investigator on the specific pneumonia eCRF. • **Pancreatitis – investigator reported**: defined as events reported on the pancreatitis eCRF. • **Pancreatitis – positively adjudicated by pancreatic adjudication committee (PAC)**: defined as events reported on the pancreatitis eCRF and adjudicated as pancreatitis by the PAC. Adjudicated as pancreatitis is defined as the probability of pancreatitis reported as definite or possible by the PAC. • **Thyroid Adverse Events – investigator reported**: Thyroid adverse events are events reported by the investigator on the specific AESI eCRF (Thyroid cancer, nodule and goiter diagnosis). • **Gastrointestinal Events**: defined as AEs coded to the MedDRA SOC of gastrointestinal disorders • **Injection Site Reaction – investigator reported**: defined as events reported by the investigator on the specific investigational product injection site reactions eCRF • **Systemic Allergic Reaction – investigator reported**: Potential systemic allergic reactions are events reported by the investigator on the specific AESI eCRF (hypersensitivity – syndrome/symptoms). • **Liver Monitoring/Stopping Events – investigator reported**: defined as events reported by the investigator on the specific liver event pages in the eCRF. Liver events as defined in the protocol. • **Liver Events**: defined as events identified by a customised MedDRA query. • **Renal Impairment – investigator reported**: defined as events reported by the investigator on the specific renal impairment eCRF. • **Diabetic ketoacidosis (DKA)**: defined as events identified by a customised MedDRA query. • **Appendicitis**: defined as events identified by a customised MedDRA query. • **Pancreatic Cancer**: defined as events identified by a customised MedDRA query. • **Malignant Neoplasms**: defined as events identified by a standard MedDRA query.
GI Events Over Time
• For the summary of GI events over time (by week), each week will include those subjects with onset of the event during that particular week and also those subjects with the event that started during a previous week but has not resolved.

Subject-Reported Hypoglycaemic Events

Reporting

- Subjects reported hypoglycaemic events in an e-diary, which will be integrated with the clinical database at the end of the study. The investigator reviewed the hypoglycaemic events and any that met the definition of an SAE were also reported as such in the SAE CRF.
- Adverse event summaries therefore do not include hypoglycaemic events, unless reported in the SAE dataset by the investigator.
- Subject-reported hypoglycaemia summaries include all reported events (on-therapy and post-therapy events).

Data selection/derivation

- Subject-reported hypoglycaemic events reported in the e-diary will be integrated into the clinical database using 3 datasets:
  - DRE (start date/time of event, end date/time of event)
  - FADRE (questions about treatment, assistance and symptoms)
  - LAB (plasma glucose reading at time of event)

- To select the e-diary subject-reported hypoglycaemic event glucose results from the laboratory dataset, select only records with visit ="HYPOGLYCAEMIC EVENT"

- In order to combine information from the different datasets for a subject's hypoglycaemia event, a combination of subject id and DREREFID must be used. The **DREREFID** variable links the components of a single hypoglycaemia event across DRE, FADRE and LAB datasets

ADA Category

- Subjects reported hypoglycaemic events will be classified as defined by the ADA Workgroup on Hypoglycaemia [Seaquist, 2013].
- **Severe Hypoglycaemia**: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration
- **Documented Symptomatic Hypoglycaemia**: an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L)
- **Asymptomatic Hypoglycaemia**: an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L)
- **Probable Symptomatic Hypoglycaemia**: an event during which symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L)
- **Pseudo Hypoglycaemia**: an event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level
- Events will be classified into ADA categories based on the following questions:
- 1. 'Did you require someone else's help to get the treatment needed?' (Yes/No)
- 2. 'Any symptoms?' (Yes/No)

Subject-Reported Hypoglycaemic Events

- 3. 'Lowest plasma glucose reading at the time of the event' (numeric value/Not Done)
- Note: Glucose readings from subject-reported hypoglycaemic events initial reported in the eDiary are identified in the laboratory dataset by VISIT='HYPOGLYCAEMIC EVENT'.
- Glucose will be presented in mmol/L. A glucose value reported in mg/dL will be converted to mmol/L by multiplying the value by 0.05551.

The ADA categories will be assigned based upon the questions above as follows:

- Severe: Required assistance (Q1) = Yes
- Documented Symptomatic: Symptoms (Q2) = Yes and Glucose reading (Q3)= ≤3.9 mmol/L
- Asymptomatic: Symptoms (Q2) = No or missing and Glucose reading (Q3) = ≤3.9 mmol/L
- Probable Symptomatic: Symptoms (Q2) = Yes and Glucose reading (Q3) = Not done
- Pseudo: Symptoms (Q2) = Yes and Glucose reading (Q3) = >3.9 mmol/L
- i.e.,

ADA classification	Required Assistance	Symptoms	Glucose Reading (mmol/L)
Severe	Yes	Any*	Any*
Documented Symptomatic	No or missing	Yes	0 < glucose ≤3.9
Asymptomatic	No or missing	No or missing	0 < glucose ≤3.9
Probable Symptomatic	No or missing	Yes	Glucose = 0 or missing
Pseudo	No or missing	Yes	Glucose >3.9

* includes missing values

- A subject reported event that does not meet any of the above criteria will not be counted as a hypoglycaemic event (any events will be flagged to the study team for review).
- Only hypoglycaemic events that subjects record in the glucose meter will be included in the summaries of subject-reported hypoglycaemic events. Glucose readings reported, for example, as part of standard laboratory testing or the 7-point glucose profile will not be included.
- Each event will be assigned to one ADA category, but a subject may report events from multiple ADA categories. A subject will appear in all ADA categories they experience.

Daytime/Nocturnal Events

- Subjects report the start date/time of a hypoglycaemia event. The start time of event will be used to classify the event as daytime or nocturnal.
- Daytime Hypoglycaemia: an event with an onset time between 06:00h and 00:00h (inclusive). i.e., in SAS time format (secs): start time = 0 or start time >21541
- Nocturnal Hypoglycaemia: an event with an onset time between 00:01h and 05:59h (inclusive). i.e., in SAS time format (secs): 0 < start time ≤21540
- Events with a missing start time will be classified as Daytime events

Time periods (3 monthly intervals)

- Events will be assigned to time periods will are defined using the following categories:
- Baseline to ≤Week 12: Study day 1 to ≤84
- >Week 12 to ≤Week 24: Study day 85 to ≤168
- >Week 24 to ≤Week 36: Study day 169 to ≤252
- >Week 36 to ≤Week 52: Study day 253 to ≤364
- >Week 52 to ≤Week 64: Study day 365 to ≤448

Time periods (2 weekly intervals)

- A summary of events by 2 weekly time periods will also be produced. E.g., Day 1 to Day 14; Day 15 to Day 28; etc.

Denominators for time period summaries

- Summaries of subject-reported events over time will calculate percentages based on the number of subjects at risk of an event within each time period. i.e., the Ns will be expected to decrease over time as subjects withdraw from the study
- The date of study withdrawal will be used as the end-date of the 'at-risk' period for each subject, as subject-reported hypoglycaemic events are reported throughout the study period i.e., until week 64 or study withdrawal.
- A subject will not be included as 'at-risk' in a particular period if their study withdrawal date is before the start date of the interval.

Hypoglycaemic Events with Glucose <3.1mmol/L

- Hypoglycaemic events with a plasma glucose <3.1 mmol/L (<56 mg/dL) will also be identified.

Laboratory Parameters

Only data from the central laboratory will be included in the tables, figures and listings. Data from local laboratories will not be included.

eGFR

- eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)
- eGFR will be calculated based on measured creatinine and associated age. For this purpose, associated age (in whole years) will be calculated with respect to the date of creatinine sample using the imputed date of birth (see Section 11.6.2.1).
- This derived eGFR will be used for summary tables.

Glucose data not included in laboratory TFLs

- Glucose readings from the MMTT will not be included in any laboratory TFLs. These are identified in SDTM.LB as LBTEST='Glucose' and LBTPTNUM = 10, 20, 30, 40, 50, 60, 70.
- Finger-stick glucose readings for the MMTT will not be included in any laboratory TFLs. These can be identified in the SDTM.LB dataset using LBTEST='Glucose' and VISIT ne '' and LBNAM='NOT APPLICABLE - NO RANGES EXPECTED', LBTPT=' ' and LBSPEC='BLOOD'.
- Glucose data from the eDiary card and 72h CGM will not be included in any laboratory TFLs. The glucose data from the eDiary and 72h CGM can be identified in the laboratory domain/dataset (SDTM.LB) as LBTEST = "Glucose" and LBNAM="NOT APPLICABLE – NO RANGES EXPECTED".
    - Subject reported Hypoglycaemic event glucose readings are identified where LBTPT

Laboratory Parameters
(timepoint) = null and visit = null [these can be identified in SI.LAB with visit="HYPOGLYCAEMIC EVENT"] o Routine glucose monitoring readings are identified where LBTPTNUM = 150, 160, 170, 180, 190, 200 corresponding to (OTHER, BEFORE MEAL, AFTER MEAL, AFTER MEDICATION, AFTER SPORT, CONTROL) o 7 Point glucose monitoring readings are identified where LBTPTNUM = 80, 90, 100, 110, 120, 130, 140 corresponding to (BEFORE BREAKFAST, 2 HRS AFTER BREAKFAST, BEFORE LUNCH, 2 HRS AFTER LUNCH, BEFORE DINNER, 2 HRS AFTER DINNER, AT BEDTIME). Data directly from the eDiary with VISIT = null. Data recorded into the eCRF with VISIT present (not null). o 72h CGM data are identified where LBSPEC='INTERSTITIAL FLUID' and LBMETHOD='TRANSDERMAL MONITORING'.
Laboratory Values Below Limits of Quantification and Repeat Testing
• Laboratory results that are beyond the limits of quantification will have the inequality sign dropped (<, ≤, >, or ≥) and the quantification limit will be used as the numeric result for summarisation.
Potential Clinical Importance (PCI)
• The categories for PCI criteria are: Low; Normal; High. • Data will be summarised by nominal visit, but will also include 'any on-therapy visit' and 'any post-baseline visit' categories. These 'any visit' categories will also include unscheduled visits. • The data is summarised using a shift table, comparing the baseline category to the worst case post-baseline category at that time-point (note, worst case is applicable for the 'any visit' categories). The percentages are based on the number of subjects in the treatment group with data for the laboratory test post-baseline at that time-point. Subjects with a missing baseline value are to be assumed to have a normal/within range baseline value. • Worst case can be either High or Low. If a subject has both a decrease 'Low' and an increase 'High', then the subject is counted in both the 'Low' and 'High' categories.
Hepatotoxicity
• Subjects falling into the following categories will be summarised: o ALT ≥3xULN and Total Bilirubin ≥2xULN o ALT ≥3xULN and INR >1.5xULN o Hepatocellular injury o Hepatocellular injury and Total Bilirubin ≥2xULN o ALT ≥3xULN, ≥5xULN, ≥8xULN, ≥10xULN, ≥20xULN, o Total Bilirubin ≥2xULN o ALP ≥2xULN and (Baseline ALP <2xULN or Baseline ALP missing) • Time from first dose of study treatment to first ALT elevation ≥3x (ULN) (days) will be calculated as: (Date of first ALT ≥3xULN) – (Date of first dose) • Further details can be found in the IDSL core standards 'Liver Event Displays'.

Vital Signs
Potential Clinical Importance (PCI)
• The categories for PCI criteria are: Low; Normal; High. • Data will be summarised by nominal visit, but will also include 'any on-therapy visit' and 'any post-baseline visit' categories. These 'any visit' categories will also include unscheduled visits. • The data is summarised using a shift table, comparing the baseline category to the worst case post-baseline category at that time-point (note, worst-case is applicable for the 'any visit' categories). The percentages are based on the number of subjects in the treatment group with data for the test post-baseline at that time-point. Subjects with missing baseline value are to be assumed to have normal/within range baseline value. • Worst case can be either High or Low. If a subject has both a decrease 'Low' and an increase 'High', then the subject is counted in both the 'Low' and 'High' categories.

11.5.4. Efficacy

Mixed Meal Tolerance Test (MMTT) Efficacy Endpoints
Stimulated (from MMTT) 2 hour plasma C-peptide AUC
• The C-peptide measurements collected during the 120 minute period following a MMTT are referred to as stimulated C-peptide values. Mixed meal stimulated C-peptide AUC is the area under the C-peptide/time curve from Time 0 to 120 minutes, calculated using the trapezoidal rule. In the computation of the AUC, time will be the nominal sampling time, which will be assigned based on the corresponding visit label in the laboratory results dataset. This reported AUC is normalized for time interval by dividing it by 120 minutes. Note, 120 minutes is used if the result at t=120 is non-missing, otherwise the time difference between first and last times with non-missing results is used. This normalized AUC will be calculated for each subject at Baseline, week 16, week 28, week 52 and week 64. Throughout this document, the term 'C-peptide AUC' refers to time normalized mixed-meal stimulated C-peptide AUC (note: this is equivalent to a weighted mean AUC). • Time normalized AUC(0-2H)/weighted mean AUC(0-2H) will be derived for C-peptide and Glucagon • Note: time point refers to the nominal sampling time from laboratory data. • The weighted mean parameters will be derived by calculating the area under the curve AUC using the trapezoidal rule, and then dividing by the nominal relevant time interval (i.e. tf – tl): • Weighted Mean (t_f-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: • yi = Value of endpoint at ith time point • ti = The ith nominal time point (mins) for MMTT: • Before MMTT : t1=0 • After MMTT : t2 =15m, t3 = 30m, t4=60m, t5=90m, t6=120m • tf = Nominal time point (hrs) of first non-missing obs (in planned time tf=0h) • tl = Nominal time point (hrs) of last non-missing obs (e.g. in planned time for Glucose, tl=120m) • I = Number of time points used in the AUC calculation (e.g. I=6) • If one or more of these assessments is missing (note: values reported as BLQ are not

Mixed Meal Tolerance Test (MMTT) Efficacy Endpoints

considered missing), AUCs will be calculated based on the non-missing data using the trapezoidal rule. If the Time 0 assessment is missing, it will be substituted with the value from the -10 minute time point. For an AUC to be calculated, there must be a minimum of one fasting data point (assessments scheduled for -10 minutes and Time 0), and one post-mixed meal data point (assessments scheduled for 15, 30, 60, 90, and 120 minutes). If this minimum number of data points is not available, the AUC will be recorded as missing.

- If the MMTT is conducted when the plasma glucose values are out of the range specified, the data will not be included in the analysis and treated as missing. Prior to the MMTT, plasma glucose will be measured using a finger-stick test and must be > 3.9 mmol/L (70 mg/dL) and ≤ 11.1 mmol/L (200 mg/dL) for the data to be included in the analysis. Only the plasma glucose values from the finger-stick test will be used to exclude data from the analysis (no other glucose values will be considered). The MMTT will be treated as missing in the summary/analyses, but will be provided in data listings (along with finger-stick test results).
- Finger-stick glucose results can be identified in the SDTM.LB dataset using LBTEST='Glucose' and VISIT ne '' and LBNAM='NOT APPLICABLE - NO RANGES EXPECTED', LBTPT=' ' and LBSPEC='BLOOD'.

Maximum Stimulated C-peptide

- This will be derived as the highest C-peptide value at any time point during the 2 hour MMTT after the subject has ingested the mixed meal.

Plasma Glucagon AUC (0-2hrs)

- This will be calculated as described for C-peptide AUC, but using the plasma glucagon measurements.
- Calculated using nominal times only.

- Change from baseline in plasma glucagon AUC (from MMTT) is a secondary endpoint. The lower limit of quantification (LLQ) for the glucagon test at study start was 0.0378 nmol/l (SI: 134.043 ng/l), but during the study this lower limit was changed to 0.0223 nmol/l (SI: 79.078 ng/l). All samples received by Q2 on or after 29th August 2015 have a lower limit of 0.0223, whereas any samples received before 29th August have a lower limit of 0.0378. A large proportion of results were reported as <LLQ (i.e. <0.0378 or <0.0223). At a subject level, if this changed mid-way through the study for an individual subject then there could be an artificial lowering of the plasma glucagon value due to the change in limit of quantification rather than any treatment effect (for example, if AUC at baseline was based on <0.0378 and at week 28 on <0.0223). For such subjects, the data is un-interpretable. The following rules will be implemented to account for this:

- Following a review of the data, the lower limit of quantification used for a sample will be assigned as: samples dated after 20th August 2015 used a lower limit of 0.0223; samples dated on or before 20th August 2015 used a lower limit of 0.0378.
- For subjects who have data assessed using the same lower limit throughout the study (either 0.0378 or 0.0223) then no changes will be made and the data will be used as recorded.
- For subjects who have baseline data recorded using the 0.0378 limit, but data for subsequent visits reported using the 0.0223 limit, then all data will be used as if reported using the original

Mixed Meal Tolerance Test (MMTT) Efficacy Endpoints

limit of 0.0378.
  - For visits using the original limit of 0.0378, data will be used as recorded.
  - For visits using the updated 0.0223 limit, any results reported with a value <0.0378 (either a numeric value between 0.0223 and 0.0378, or a value reported as <0.0223) will be changed so the data used is included as <0.0378. Any results with a value ≥ 0.0378 will remain unchanged.
- Although described in terms of original units here, data will be summarised using SI units.

Other Efficacy Endpoints

HbA1c

- HbA1c will be summarised as reported from the central laboratory with units as % of total haemoglobin.
- In addition, summary statistics will be produced for HbA1c with units of mmol/mol.
- For HbA1c measured in mmol/mol, values can be converted to % based on the following [Geistanger, 2008; Hoelzel, 2004]:
  HbA1c (%) = [0.09148 * HbA1c (mmol/mol)] + 2.152
- Therefore, for HbA1c measured in %, values will be converted to mmol/mol based on solving the above equation as follows:
  HbA1c (mmol/mol) = [HbA1c (%) – 2.152] / 0.09148

Exogenous Insulin Use (Mean Daily Insulin Use)

- Mean Daily Insulin Use
- In a change to the planned derivation specified in the protocol:
- In this section, the term “mean daily insulin use” will refer to mean total daily insulin dose per kg body weight. The mean total daily insulin dose per kg body weight will be computer as the sum of average prandial insulin doses and average of basal insulin doses for each subject recorded daily for the three days prior to the specified visits, divided by the subject’s body weight in kg, using the most recently obtained weight measurement.
- Subjects will record their daily insulin use in an electronic diary. This information will be transferred to the concomitant medications dataset. Insulin usage is made up of two types – long-acting (basal) and meal-time (prandial) insulin. Both types will be included when calculating daily insulin usage. Data will be identified using the variable CMTYPCD (‘192’=Long-acting insulin and ‘193’=Meal-time insulin).
- This information will be collected for at least 3 days before Baseline, daily for the first 2 weeks and for at least 3 days preceding the telephone calls/visits at Week 3 through to Week 16, Week 22, Week 28, Week 34, Week 40, Week 46, Week 52 and Week 64. Only data at Baseline, Week 4, 8, 16, 28, 40, 52 and 64 will be included in summary tables and analyses. Data from all time points will be listed.
- Only data from the 3 days immediately preceding the study visit will be used in calculation of mean daily insulin, even if more than 3 days of data are recorded. See Section 11.2.2.
- A subject’s mean daily insulin use will be calculated as follows:
- Mean total daily insulin use (units/kg/day) =(Average long-acting insulin over the 3 consecutive days + average meal-time insulin over the 3 consecutive days)/body weight (kg)
- Calculations at each time point will use the most recently obtained weight. To select the most

Other Efficacy Endpoints

recently obtained weight for adjustment of mean total daily insulin dose at a visit, measurements up to and including the visit are considered.

- For calculations of the average meal-time insulin (prandial):
  - a subject must have non-missing insulin doses (i.e., dose of 0 or above) for breakfast, lunch and dinner for a day to be included in the calculations.
  - It is the total meal-time insulin for each day that is used in calculations.
- For calculations of the average long-acting insulin (basal):
  - For a day to be included in the calculations, a subject must have at least one non-missing long acting insulin dose (0 mg dose counts as non-missing, as the subject has confirmed no dose). If a day has any missing doses of long-acting insulin recorded then it will not be included in the calculations, even if it also has non-missing doses recorded.
- The evaluability of data from each of the 3 days is defined separately for average meal-time insulin and average long-acting insulin. The average for each insulin parameter is then calculated using only data from the evaluable days and using the number of evaluable days, for each insulin parameter respectively.
- The average total daily insulin dose will be the sum of the average meal-time insulin and the average long-acting insulin at each visit. If either the average mealtime insulin or the average long-acting insulin is unevaluable then the total daily insulin will be unevaluable.
- This total will then be adjusted by dividing by the most recent body weight (kg)

Responders

- A subject will be considered a responder if, at a given visit, the subject 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 subject is classed as a responder or not

Partial Remission Status

- A subject achieving partial remission status is defined as a subject with Insulin Dose Adjusted A1c (IDAA1C) ≤9.0 [Mortensen, 2009].
- 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.

Subject-Reported Hypoglycaemic Events (Efficacy)

- Subject-reported hypoglycaemic event data collection and derivation is described in Section 11.5.3
- Significant hypoglycaemia is defined as events with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and/or requiring third party intervention. This corresponds to ADA category definitions of severe hypoglycaemia, documented symptomatic hypoglycaemia and asymptomatic hypoglycaemia.
- Events will be assigned to time periods based on the date of event:

Other Efficacy Endpoints

- Baseline to Week 24: study day 1 to study day 168
- >Week 24 to ≤Week 52: study day 169 to study day 364
- The number of significant hypoglycaemic events that each subject experienced in each time period will be calculated.

7 point Glucose Profile

- Data from the 7-point blood glucose profile page in the eCRF will be used for this endpoint. Data recorded from the glucose meter to the electronic diary will not be used.
- The schedules collection times for the 7-point glucose profile are: before breakfast (at least 8 hours without food intake); 2 hours after breakfast; before lunch; 2 hours after lunch; before dinner; 2 hours after dinner; at bedtime.
- Glucose will be presented in mmol/L. A glucose value reported in mg/dL will be converted to mmol/L by multiplying the value by 0.05551.
- The 7-point glucose profile will be assessed at Baseline, Week 28 and Week 52.
- All non-missing data will be included in the summaries of glucose levels at each of the 7 specified time-points (before breakfast, 2 h after breakfast, etc.).
- To be evaluable for the endpoints relating to number and magnitude of hypo/hyperglycaemic excursions (endpoints detailed below) the following rules will apply:
    - A subject with non-missing glucose values for at least 4 of the 7 scheduled time-points will be evaluable for hypoglycaemic excursions and hyperglycaemic excursions
    - A subject with <4 non-missing glucose values will be evaluable for hypoglycaemic excursions **only** if one or more of the non-missing glucose values is a hypoglycaemic excursion (i.e., blood glucose level is ≤3.9 mmol/L)
    - A subject with <4 non-missing glucose values will be evaluable for hyperglycaemic excursions **only** if one or more of the non-missing glucose values is a hyperglycaemic excursion (i.e., blood glucose level is >10.0 mmol/L)
- Subjects will be determined as evaluable for hypoglycaemic excursions and hyperglycaemic excursions separately at each visit, based on the non-missing data reported at that visit.
- At Baseline, Week 28 and Week 52, the following parameters will be calculated for each subject:
- **Hypoglycaemic Excursions:** A hypoglycaemic excursion is defined as an occurrence where the blood glucose level is ≤3.9 mmol/L (i.e. ≤70 mg/dL)
- Any hypoglycaemic excursions (yes/no)
- Number of hypoglycaemic excursions (e.g. expected 0 -7)
- Greatest hypoglycaemic excursion: this will be calculated as 3.9 mmol/L minus the lowest recorded glucose level during the 7-point glucose profile. If a subject has data recorded in the interval, but does not have a value ≤3.9 mmol/L, the subject's greatest hypoglycaemic excursion for that interval would be 0 mmol/L.
- **Hyperglycaemic Excursions**: A hyperglycaemic excursion is defined as an occurrence where the blood glucose level is >10.0 mmol/L (i.e. >180 mg/dL)
- Any hyperglycaemic excursions (yes/no)
- Number of hyperglycaemic excursions (e.g. expected 0 -7)
- Greatest hyperglycaemic excursion: this will be calculated as the largest recorded glucose level during the 7-point glucose profile minus 10.0 mmol/L. If a subject has data recorded in the

Other Efficacy Endpoints

interval, but does not have a value >10.0 mmol/L, the subject's greatest hyperglycaemic excursion for that interval would be 0 mmol/L.

72 hour CGM

- Glucose variability is also assessed using continuous glucose monitoring (CGM), where glucose is sampled every 5 mins for 72 hours. 72-hour CGM will be performed at baseline, week 28 and week 52.
- At each time point the following parameters will be calculated for each subject:
    - Time spent with a plasma glucose ≤3.9 mmol/L
    - Time spent with a plasma glucose between >3.9 and 10.0 mmol/L
    - Time spent with a plasma glucose >10.0 mmol/L
- Data will be derived as follows:
- A subject must have at least 24 hours of CGM data recorded in order to be considered evaluable (note, this does not need to be in one continuous period)
- If a value of x is recorded at time 0, a value of y at time 5 mins, and a value of z at time 10 mins then a subject will be considered to have a plasma glucose level of x from time 0-5 (5mins); a value of y from time 5-10 (5mins); a value of z from time 10-15 (5mins); etc.
- Each 5 minute time period will be assigned to time spent ≤3.9 mmol/L, between >3.9 and 10.0 mmol/L and >10.0 mmol/L.
- Data for each subject will be summed into the 3 categories, over the time period they have available, so they have:
    - Actual time spent ≤3.9 mmol/L,
    - Actual time spent between >3.9 and 10.0 mmol/L
    - Actual time spent >10.0 mmol/L.
    - Total actual time
- To calculate the actual time spent within each range, each CGM observation will be assigned as ≤3.9 mmol/L, between >3.9 and 10.0 mmol/L, and >10.0 mmol/L. The number of observations within each range will be summed, and the total number of observations within each range will be multiplied by 5 minutes to calculate the actual time within each range.
- The total actual time is the sum of the actual time spent within each range for the 3 ranges.
- There may be periods of missing data within the 72h CGM. As it is unknown what the plasma glucose value was during these times, they will be excluded from calculations.

For each category, data will be converted into time spent for a 24 hour period as follows:

- Time spent ≤3.9 mmol/L (hours/24h) = Actual time spent ≤3.9 mmol/L / Total actual time * 24
- Time spent between >3.9 and 10.0 mmol/L (hours/24h) = Actual time spent between >3.9 and 10.0 mmol/L / Total actual time * 24
- Time spent >10.0 mmol/L (hours/24h) = Actual time spent >10.0 mmol/L / Total actual time * 24
- The time spent in each of the 3 glycaemic state for a 24h period should sum to 24h for each subject.
- For each category, change from baseline will be calculated using the time spent for a 24 hour period (hours/24h)
- In addition, the time spent in each of the 3 glycaemic states will be calculated as a percentage e.g.

  Time spent ≤3.9 mmol/L (hours/24h) = Actual time spent ≤3.9 mmol/L / Total actual time * 100

11.5.5. Exploratory Endpoints

Exploratory Endpoints
Urinary C-peptide 120 minutes after a mixed meal (urinary creatinine corrected)
• Urinary C-peptide from the MMTT will be corrected for urinary creatinine and will be provided in the data as the urinary C-peptide creatinine ratio parameter. • No derivation necessary. • The protocol statistical section refers to this variable as 120 minutes urinary C-peptide AUC, however for consistency with how the parameter is calculated it will be referred to as the urinary C-peptide creatinine ratio.
Audit of Diabetes Dependent Quality of Life (ADDQoL)
• The ADDQoL is a validated instrument for the assessment of the impact of diabetes on quality of life. The ADDQoL 19 will be used in this trial. • The ADDQoL consists of two overview items designed for audit purposes: o generic 'Present QoL' o diabetes-specific 'Impact of diabetes on QoL' • These two overview items will be scored individually. • The general overview item is measured on a 7-point scale where -3 represents extremely bad and +3 represents excellent (e.g., from −3 to +3). • The diabetes-specific overview item is measured on a 5-point scale of −3 (maximum negative impact of diabetes) to + 1 (maximum positive impact of diabetes). • A further 19 items assess the impact of diabetes on a range of quality of life domains: o Leisure activities o Working life o Journeys o Holidays o Physical health o Family life o Friendships and social life o Personal relationship o Sex life o Physical appearance o Self-confidence o Motivation o People's reactions o Feelings about the future o Financial situation o Living conditions o Dependence on others o Freedom to eat o Freedom to drink • Respondents rate both impact of diabetes on applicable domains and also the importance of those domains for their QoL. Respondents also indicate if some domains are not relevant to them. The instrument thus yields a weighted global score calculated only on domains relevant

Exploratory Endpoints

to the respondent, in addition to individual domain and overview item scores.

- All 19 questions are measured on a 5-point scale, ranging from −3 (greatest negative impact) to +1 (greatest positive impact).
- Subjects are also required to give an "importance score" rating for these 19 domains on a 4-point scale, from 0 (not at all important) to 3 (very important).
- The option of "non-applicable" is included in five of the domains (working life, holidays, family life, close personal relationship and sex life) if it is considered to be irrelevant by the subjects
- The weighted impact score is calculated by multiplying the importance scores and impact scores. The average weighted impact score is obtained by averaging all the weighted scores and is interpreted as the overall weighted impact score of DM on quality of life.

Scoring

- *Two overview items*: scored individually
- *Individual domains*: scores
    - Impact rating (score -3 to +1)
    - Importance rating (score 0 to 3)
- *Individual domains:* a weighted score for each domain is calculated as follows:
    - Weighted impact score=impact rating (score -3 to +1) x importance rating (score 0 to 3)
    - Score -9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes)
    - NB: 'Unimportant' domains score 0, regardless of magnitude of impact of diabetes. Domains with no impact of diabetes score 0, regardless of their importance to QoL. Any non-applicable domains are not scored.
- *Average weighted impact score*:
    - = sum of weighted ratings of applicable domains / N of applicable domains

Score -9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes)

- Although described here for completeness, weighted scores will not be derived, either overall or for individual domains. Only data as collected in the ADDQoL will be listed, with no further derivation.

11.5.6. Immunogenicity

Immunogenicity

- Immunogenicity was assessed at Baseline, Week 2, 4, 6, 8, 16, 28, 40, 52 and 64
- The following antibodies will be assessed:
    - Anti-albiglutide antibody
    - Anti-GLP-1 antibody
    - Anti-HA (Albumin) antibody
    - Anti-albiglutide neutralising antibody
- Note, only anti-albiglutide antibody positive samples will be analysed for the other antibodies
- Results will be assessed as positive or negative.
- [Note: the positive/negative result will be provided in the data, not derived by programming]
- For testing that includes confirmatory analyses, subjects are considered antibody positive if both the screening and confirmatory results were positive; antibody negative subjects are those with a negative screening result or a positive screening result but a negative confirmatory result. For testing that includes confirmatory analyses, subjects with a positive screening result, but no confirmatory result (i.e. test not done) will be considered unknown antibody status. For the anti-HA antibody, subjects are considered antibody positive or negative based on the screening result, since confirmatory testing is not performed. Results reported as "Not applicable" are not considered informative and are equivalent to missing for purposes of summaries and listing.
- In addition, anti-albiglutide positive samples will be titrated to obtain the titre of antibodies (anti-albiglutide antibody titre and anti-albiglutide neutralising antibody titre). These will be provided as numeric values (0 dps).

- Additionally, for subjects who experience systemic allergic reactions that include anaphylaxis, a sample will be taken at a time as close as possible to the event. The sample will be tested for albiglutide-specific IgE antibody, including the titre level. These results will not be summarised, but will be presented in data listings.

- Anti-albiglutide antibody positive subjects are defined as subjects with an anti-albiglutide antibody result of positive at any visit (including those with a positive result at baseline, regardless of whether they had a positive post-baseline result). Anti-albiglutide negative subjects are defined as those subjects with an anti-albiglutide antibody result of negative at all visits. The result derived from screening and confirmatory results (where applicable) will be used for this assessment.

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

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completion of all periods of the study up to and including the follow-up period. • The protocol specified that 'if the withdrawal rate from the study is larger than expected, consideration will be given to replacing subjects who withdraw from the study.'. However due to poor enrolment a decision was made that withdrawn subjects would not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

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 subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

11.6.2.1. Handling of Missing or Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
General, including Concomitant Medications	In general partial dates will be imputed as follows: A partial event start date, partial start dates of prior and concomitant medications or partial diagnosis date will be assumed to be the earliest possible date consistent with the partial date. • If year is missing, the year will be assumed to be the year part of informed consent date of that subject; • If month is missing, the month will be assumed to be January; • If day is missing, it will be assumed to be the first day of the month • In the case of completely missing start date, the start date will be assumed to be prior to date of the first administration of study medication. Partial event or medication stop dates will be assumed to be the latest possible date consistent with the partial date. • If month is missing, it will be assumed to be December; • If day is missing, it will be assumed to be the last day of the month • In the case of completely missing stop date, the stop date will be assumed to be after the date of the last study visit; the event or medication are assumed to be ongoing.
Adverse Events	For AE date imputation this general rule will be followed but will be more conservative in nature consistent with the therapy phase. For an AE with an incomplete start date where the year and month are present while the day is missing, or where the year is present while both month and day are missing, the date is imputed in a dynamic way consistent with the partial date information so that the resulting AE therapy period assignment based on the imputed date is the most conservative possible, where the order from the most to the least conservative is: on-therapy phase > post-therapy phase > pre-therapy (Section 11.3) . Note that if the AE stop date is present, the imputed start date will always be on or prior to the stop date. This dynamic imputation means that if the results of imputation result in a date prior to treatment start date and the event could possibly have occurred during treatment from the partial information, then the treatment start date will be assumed to be the AE start date. The AE will then be considered to have started on-treatment (worst-case. If an adverse event start date is completely missing - it should be imputed as the treatment start date. So the event would be considered on-therapy (worst-case).
Date of Birth	Only the year of birth is recorded for subjects in this study, the age of the subjects for analysis purposes is calculated using June 30 of the birth year as the imputed subject birth date.

11.6.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
LOCF	• With LOCF, missing values would be carried forward from the previous, non-missing available on-treatment assessment. • The protocol specified that 'In analyses of HbA1c and insulin usage, missing data at key analysis time points will be imputed using the last observation carried forward method.' • In a change to the planned analysis, the last observation carried forward method will not be used for HbA1c and insulin usage. • Therefore the LOCF method is not used in this study for any endpoints or analyses.
Responder analysis and Partial Remission Status analysis	• A post-hoc sensitivity analysis imputing missing data may be performed if needed, but is not currently planned to be performed. If a subject has missing HbA1c/insulin use data and the reason why the value is missing is not related to efficacy or safety (e.g., procedural) and could be assumed that the value is missing at random, then the value would be left as missing for calculations; if the reason why the value is missing is lack of efficacy or due to safety, then this missing value would be imputed as 'not meeting target' and included in the denominator in the calculations of the proportion of responders. • Reasons for study withdrawal of adverse event (excluding pregnancy) would be considered as potentially missing due to lack of efficacy or safety. • Reasons for study withdrawal of lost to follow, investigator discretion or withdrew consent would be reviewed and further information from sites investigated, to determine if these should be considered as potentially missing due to lack of efficacy or safety. • Reasons for study withdrawal of pregnancy, protocol deviation, study closed/terminated or investigator site closed would be considered as missing at random
MMRM analyses	• Missing data are not explicitly imputed in MMRM analyses; although there is an underlying assumption that data are missing at random, including those withdrawn for lack of efficacy. The MMRM method will produce an unbiased estimate of treatment effect under the missing at random (MAR) assumption. Under a MAR assumption where the missing data may depend on the prior observations, i.e., the conditional independence assumption, the model provides unbiased LSmean estimates for the treatment groups at the assessment time points

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)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

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

11.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		≥ 500
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Absolute Heart Rate	bpm	< 50	> 120
Change from Baseline			
Increase from Baseline QTc	msec		≥ 60
Increase from Baseline PR Interval	msec		>50% when baseline PR≤200 msec
Increase from Baseline QRS Interval	msec		>50% when baseline QRS≤100 msec

Note: PCI will be assessed for QTc using QTcF values. In cases where QTcF is not reported and is unable to be derived, then PCI will be assessment using the value of QTc (other method of correction). Data will be presented separately for the two QT correction methods.

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

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

11.8. Appendix 8: Examination of Covariates, Subgroups & Other Strata

11.8.1. Handling of Covariates, Subgroups & Other Strata

- The following is a list of covariates that may be used in statistical analyses
- Additional covariates of clinical interest may also be considered.
- Due to the small sample size of the study and the 3:1 randomisation ratio, there are no planned subgroup analyses in this study.

Category	Covariates
Age (continuous)	Age (years) Calculated as age at randomisation.
Age (categorical)	Age will be dichotomised into a binary variable, based on whether a subject's age is above or below the median age (overall subjects in the ITT population). < median age (years) ≥median age (years) Calculated using age at randomisation.

NOTES :

- Age will be included as a continuous covariate where possible. Some analyses may use age as a categorical covariate, if necessary.

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

11.9.1. Statistical Analysis Assumptions

Endpoint(s)	• Change from baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 52
Analysis	• Bayesian analysis
• Convergence will be assessed as described in Section 7.1.2.	

Endpoint(s)	• Change from baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC • Change from baseline in maximum stimulated plasma C-peptide • Change from baseline in plasma Glucagon AUC (from MMTT) • Change from baseline in HbA1c (%) • Change from baseline in body weight (kg) • Change from baseline in time spent (h/day) with plasma glucose ≤3.9 mmol/L at Week 28 and Week 52; • Change from baseline in time spent (h/day) with plasma glucose between >3.9 and 10.0 mmol/L at Week 28 and Week 52; • Change from baseline in time spent (h/day) with plasma glucose >10.0 mmol/L at Week 28 and Week 52;
Analysis	• MMRM

- Model assumptions will be applied, but appropriate adjustments maybe made 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 Compound Symmetry Heterogeneous (CSH) or Compound Symmetry (CS).
    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data or appropriate non-parametric methods may be explored.

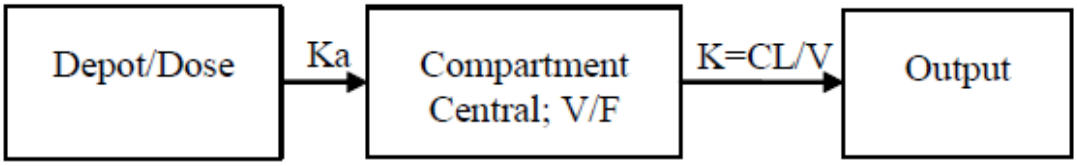
11.10. Appendix 10: Population Pharmacokinetic Analyses

11.10.1. Population PK modelling

Based on the pharmacokinetic profile of GSK716155 from previous clinical studies conducted in healthy volunteers and patients with Type 2 diabetes mellitus a Population PK model has been previously developed. The one-compartment PK model assumes a first order absorption and accounts for the drug's elimination processes.

A schematic of the one-compartment PK model is displayed in Figure 1.

Figure 1 The One-Compartment Pharmacokinetic Model



where,

V/F (V) = apparent volume of distribution

Ka = first order absorption rate

K = first order elimination rate constant

CL/F (CL) = clearance

The model will be parametrized in terms of the key population parameters CL/F, V/F, and Ka.

Creatinine clearance will be calculated and provided for population PK modelling only. Estimated creatinine clearance (eCrCl) in units of ml/min will be calculated using the Cockcroft-Gault formula as follows:

eCrCl = [(140 – age in years) x (weight in kg) x 0.85 (if female)] / (72 x serum creatinine in mg/dl)

For this purpose, associated age (in whole years) will be calculated with respect to the date of creatinine sample using the imputed date of birth (see Section 11.6.2.1).

Other data provided for population PK purposes will include demographic and baseline characteristics, other laboratory parameters and information on insulin use.

11.11. Appendix 11: Mixed Meal Tolerance Test (MMTT) – Supplementary Information

The MMTT will be performed according to the schedule in the Time and Events Table (see Section 11.1 and study protocol). Further details on the procedure are provided in the SPM.

For the 3 days before the MMTT, subjects will be asked to eat a balanced diet consistent with advice provided by a nutritionist or dietitian and/or diabetes educator according to the local institution's guidelines for NOT1DM and not to make major changes from their customary exercise regimens.

On the evening before the MMTT, subjects should eat a full, usual meal, then fast from 21:00 h (9 PM) until the MMTT is completed. Water, black coffee, or black tea (with no sugar or artificial sweeteners) is allowed during the fast and test.

The MMTT will start in the morning and the time the test is started should be kept as consistent as possible. Prior to the test, plasma glucose will be measured using a finger-prick test and must be >3.9 mmol/L (70 mg/dL) and ≤11.1 mmol/L (200 mg/dL) for the MMTT to be performed. If the glucose is outside this range, the MMTT must be rescheduled.

On the morning of the test, subjects will modify their insulin regimen as follows:

- Withhold the morning dose of long- or intermediate-acting insulin
- No short-acting insulin for at least 6 hours before the test
- No rapid-acting insulin for at least 2 hours before the test

Immediately prior to the test, subjects should void their bladder.

Subjects will consume a standardised amount of a nutritional drink (6 mL per kg body weight up to a maximum of 360 mL). The time when the subject starts drinking is defined as Time 0. The subject will drink the nutritional drink within 5 minutes or less.

Blood samples will be taken to assess levels of C-peptide, glucose and glucagon at

- 10 minutes before Time 0 (-10 minutes).
- Immediately before the subject starts drinking the nutritional drink (Time 0).
- 15, 30, 60, 90, and 120 minutes after Time 0.

A urine sample will be taken at 120 minutes after Time 0 to assess C-peptide and creatinine.

A snack appropriate for a subject with diabetes will be available immediately after the 120-minute blood draw. As soon as feasible after completing the MMTT, subjects will resume their usual insulin and diet regimens.

11.12. Appendix 12 – Abbreviations & Trade Marks

11.12.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADDQoL	Audit of Diabetes Dependent Quality of Life
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase (SGPT)
Anti-GAD	Antibody to glutamic acid decarboxylase
Anti-IA-2	Antibody to protein tyrosine phosphatase-like protein
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
A&R	Analysis and Reporting
BMI	Body Mass Index
BLQ	Below level of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMQ	Customised MedDRA Query
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b	Coefficient of Variation (Between)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
GSK	GlaxoSmithKline
GUI	Guidance
IA	Interim Analysis
IAA	Insulin autoantibody
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
Kg	Kilogram
LLQ	Lower limit of quantification
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
MMTT	Mixed Meal Tolerance Test
msec	Millisecond
NQ	Non-quantifiable concentration measured as below LLQ

Abbreviation	Description
PAC	Pancreatitis Adjudication Committee
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTc	QT duration corrected
QTcF	Fredericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model
SI	System Independent
SMQ	Standard MedDRA Query
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
ULN	Upper limit of normal
ULQ	Upper limit of quantification
UK	United Kingdom

11.12.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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MedDRA
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11.13. Appendix 13: List of Data Displays

11.13.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Pharmacodynamic and / or Biomarker	5.1 to 5.n	5.1 to 5.n
Pharmacokinetic / Pharmacodynamic	6.1 to 6.n	6.1 to 6.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

11.13.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 14: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

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

11.13.3. Deliverable [Priority]

SAC [X]	Final Statistical Analysis Complete

NOTES:

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

11.13.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, GSK CTR, FDAAA, EudraCT	SAC [1]
1.2.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC [1]
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures	Journal Requirements	SAC [1]
1.4.	Randomised	NS1	Summary of Subjects Randomised by Country and Site ID	EudraCT/clinical operations	SAC [1]
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [1]
1.6.	Safety	IE1	Summary of Inclusion and Exclusion Criteria Deviations		SAC [1]
Populations Analysed					
1.7.	Screened	SP1	Summary of Study Populations	IDSL	SAC [1]
1.8.	Randomised	SP2A	Summary of Exclusions from the Study Populations	IDSL	SAC [1]
Demographic and Baseline Characteristics					
1.9.	Safety	DM1	Summary of Demographics and Baseline Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	SAC [1]
1.10.	ITT	DM1	Summary of Demographics and Baseline Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	SAC [1]
1.11.	PK	DM1	Summary of Demographics and Baseline Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	SAC [1]
1.12.	Randomised	DM11	Summary of Age Ranges	EudraCT	SAC [1]
1.13.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, GSK CTR, FDAAA, EudraCT	SAC [1]
1.14.	Safety	SU1	Summary of Substance Use		SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.15.	DEFEND-1 subjects	DM1	Summary of Demographics and Baseline Characteristics (DEFEND-1 subjects)		SAC [1]
Medical History					
1.16.	Safety	MH1 or Metabolic 1.1	Summary of Past Medical Conditions	ICH E3	SAC [1]
1.17.	Safety	MH1 or Metabolic 1.1	Summary of Current Medical Conditions	ICHE3	SAC [1]
1.18.	Safety	MH1 or Metabolic 1.1	Summary of Medical/Surgical Procedure History		SAC [1]
1.19.	Safety		Summary of Family History of Cardiovascular Risk Factors, Pancreatitis and Thyroid Cancer		SAC [1]
Prior and Concomitant Medications					
1.20.	Safety	CM1	Summary of Prior Medications	By ATC level 1 and ingredient.	SAC [1]
1.21.	Safety	CM1	Summary of Concomitant Medications	ICH E3 By ATC level 1 and ingredient.	SAC [1]
1.22.	Safety	CM1	Summary of Post-therapy Medications	By ATC level 1 and ingredient.	SAC [1]
Exposure and Treatment Compliance					
1.23.	Safety	Metabolic 15.1, GLP113121, Harmony	Summary of Study Treatment Exposure	ICH E3	SAC [1]
1.24.	Safety	GLP112756	Summary of Study Treatment Titrations		SAC [1]
1.25.	Safety	GLP113121, Switch	Summary of Study Treatment Compliance		SAC [1]

11.13.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
MMTT Endpoints					
2.1.	ITT	New	Summary of MMRM Analysis of Change from Baseline in C-Peptide AUC [nmol/L] (MMTT) at Week 52: Bayesian Primary Analysis (w=0.5)		SAC [1]
2.2.	ITT	New	Statistical Output Supporting the MMRM Analysis of Change from Baseline in C-Peptide AUC [nmol/L] (MMTT) at Week 52: Bayesian Primary Analysis (w=0.5)		SAC [1]
2.3.	ITT	New	Summary of MMRM Analysis of Change from Baseline in C-Peptide AUC [nmol/L] (MMTT) at Week 52: Bayesian Sensitivity analysis without historical placebo data (w=0)		SAC [1]
2.4.	ITT	New	Summary of MMRM Analysis of Change from Baseline in C-Peptide AUC [nmol/L] (MMTT) at Week 52: Bayesian Sensitivity analysis using 100% historical placebo data (w=1)		SAC [1]
2.5.	ITT	New	Summary Statistics for C-Peptide AUC [nmol/L] (MMTT) at Week 52 for Placebo and Historical DEFEND-1 Placebo data		SAC [1]
2.6.	ITT	Metabolic 6.1, Switch, GLP113121 [A]	Summary Statistics for C-Peptide AUC [nmol/L] (MMTT) by Visit	Absolute & change from baseline	SAC [1]
2.7.	ITT	Metabolic 17.1, Switch, GLP113121 [B]	Summary of MMRM Analysis of Change from Baseline in C-Peptide AUC [nmol/L] (MMTT) over Time	Week 16, 28, 52 and 64	SAC [1]
2.8.	ITT	As above [A]	Summary Statistics for Maximum Stimulated C-Peptide [nmol/L] (MMTT) by Visit		SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.9.	ITT	As above [B]	Summary of MMRM Analysis of Change from Baseline in Maximum Stimulated C-Peptide [nmol/L] (MMTT) over Time	Week 28 and 52	SAC [1]
2.10.	ITT	As above [A]	Summary Statistics for Plasma Glucagon AUC [NG/L] (MMTT) by Visit		SAC [1]
2.11.	ITT	As above [B]	Summary of MMRM Analysis of Change from Baseline in Plasma Glucagon AUC [NG/L] (MMTT) over Time	Week 28 and 52	SAC [1]
Other Efficacy Endpoints					
2.12.	ITT	To do, Metabolic 11.1, Switch, Harmony	Summary of Responders (Proportion of Subjects Achieving HbA1c ≤7.0% and Mean Daily Insulin Use <0.5 units/kg/day) over Time	Week 4, 8,16, 28, 40, 52, 64	SAC [1]
2.13.	ITT	To do, Metabolic 11.2, Switch, Harmony	Summary of Responder Analysis (Proportion of Subjects Achieving HbA1c ≤7.0% and Mean Daily Insulin Use <0.5 units/kg/day) over Time	Week 28 and 52	SAC [1]
2.14.	ITT	To do, Metabolic 11.1, Switch, Harmony	Summary of Partial Remission Status (Proportion of Subjects achieving IDAA1C ≤9.0) over Time	Week 4, 8,16, 28, 40, 52, 64	SAC [1]
2.15.	ITT	To do, Metabolic 11.2, Switch, Harmony	Summary of Partial Remission Status Analysis (Proportion of Subjects achieving IDAA1C ≤9.0) over Time	Week 28 and 52	SAC [1]
2.16.	ITT	As above [A]	Summary Statistics for HbA1c (%) by Visit		SAC [1]
2.17.	ITT	As above [A]	Summary Statistics for HbA1c (mmol/mol) by Visit		SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	ITT	As above [B]	Summary of MMRM Analysis of Change from Baseline in HbA1c (%) over Time	Week 28 and 52	SAC [1]
2.19.	ITT	As above [A]	Summary Statistics for Mean Daily Insulin Use [units/kg/day] by Visit		SAC [1]
2.20.	ITT	As above [B]	Summary of MMRM Analysis of Change from Baseline in Mean Daily Insulin Use [units/kg/day] over Time	Week 28 and 52	SAC [1]
2.21.	ITT	New template needed	Summary of Subject-Reported Significant Hypoglycaemia by Time Period	Baseline to Week 24; >Week 24 to ≤Week 52	SAC [1]
2.22.	ITT	New template needed	Summary of Subject-Reported Significant Hypoglycaemia Occurring >Week 24 and ≤Week 52		SAC [1]
2.23.	ITT	New template needed	Summary of Glucose Levels [mmol/L] at each of the 7 specified timepoints from the 7-point Glucose Profile over Time		SAC [1]
2.24.	ITT	New, see DEFEND-1	Summary of Number (%) of Subjects with Hypoglycaemic Excursions from 7-point Glucose Profile over Time	Baseline, Week 28, 52	SAC [1]
2.25.	ITT	New, see DEFEND-1	Summary of Number of Hypoglycaemic Excursions for Each Subject from 7-point Glucose Profile over Time	Baseline, Week 28, 52	SAC [1]
2.26.	ITT	New, see DEFEND-1	Summary of Greatest Magnitude of Hypoglycaemic Excursion for Each Subject from 7-point Glucose Profile over Time	Baseline, Week 28, 52	SAC [1]
2.27.	ITT	New, see DEFEND-1	Summary of Number (%) of Subjects with Hyperglycaemic Excursions from 7-point Glucose Profile over Time	Baseline, Week 28, 52	SAC [1]
2.28.	ITT	New, see DEFEND-1	Summary of Number of Hyperglycaemic Excursions for Each Subject from 7-point Glucose Profile over Time	Baseline, Week 28, 52	SAC [1]
2.29.	ITT	New, see DEFEND-1	Summary of Greatest Magnitude of Hyperglycaemic Excursion for Each Subject from 7-point Glucose Profile over Time	Baseline, Week 28, 52	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.30.	ITT	New template needed	Summary Statistics for Time Spent with Plasma Glucose Level [mmol/L] ≤3.9, >3.9 to ≤10.0, and >10.0 (72h CGM) by Visit	Absolute & change from baseline Baseline, Week 28, 52	SAC [1]
2.31.	ITT	New template needed	Summary of MMRM Analysis of Change from Baseline in Time Spent (hours/day) with Plasma Glucose Level [mmol/L] ≤3.9, >3.9 to ≤10.0, and >10.0 (72h CGM) Over Time	Week 28, 52	SAC [1]
2.32.	ITT	As above [A]	Summary Statistics for Body Weight [kg] by Visit	Week 2, 4, 6, 8,16, 28, 40, 52, 64	SAC [1]
2.33.	ITT	As above [B]	Summary of MMRM Analysis of Change from Baseline in Body Weight [kg] over Time	Week 28 and 52	SAC [1]

11.13.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
MMTT Endpoints					
2.1.	ITT	New	Plot of Posterior Distribution of C-Peptide AUC [nmol/L] (MMTT) Treatment Difference (Albiglutide – Placebo): Bayesian Primary Analysis (w=0.5)		SAC [1]
2.2.	ITT	Metabolic 6.2, Switch, GLP113121 [C]	Line Graph of Mean (± SE) for C-peptide AUC [nmol/L] (MMTT) by Visit		SAC [1]
2.3.	ITT	Metabolic 6.3, Switch, GLP113121 [D]	Line Graph of Mean Change from Baseline (± SE) for C-peptide AUC [nmol/L] (MMTT) by Visit		SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	ITT	As above [C]	Line Graph of Mean (± SE) for Maximum Stimulated C-Peptide [nmol/L] (MMTT) by Visit		SAC [1]
2.5.	ITT	As above [C]	Line Graph of Mean (± SE) for Plasma Glucagon AUC [NG/L] (MMTT) by Visit		SAC [1]
Other Efficacy Endpoints					
2.6.	ITT	To do, Metabolic 11.9	Bar Chart of Responders (Proportion of Subjects achieving HbA1c ≤7.0% and mean daily insulin use <0.5 units/kg/day) over Time		SAC [1]
2.7.	ITT	To do, Metabolic 11.9,	Bar Chart of Partial Remission Status (Proportion of Subjects achieving IDAA1C ≤9.0) over Time		SAC [1]
2.8.	ITT	As above [C]	Line Graph of Mean (± SE) for HbA1c (%) by Visit		SAC [1]
2.9.	ITT	As above [C]	Line Graph of Mean (± SE) for Mean Daily Insulin Use [units/kg/day] by Visit		SAC [1]
2.10.	ITT	New, pie chart	Pie Chart Showing Time Spent (hours/day) with Plasma Glucose Level [mmol/L] ≤3.9, >3.9 to ≤10.0, and >10.0 (72h CGM) by Visit		SAC [1]
2.11.	ITT	New, bar chart	Bar Chart Showing Mean Change from Baseline in Time Spent (%) with Plasma Glucose Level [mmol/L] ≤3.9, >3.9 to ≤10.0, and >10.0 (72h CGM) by Visit		SAC [1]
2.12.	ITT	As above [C]	Line Graph of Mean (± SE) for Body Weight [kg] by Visit		SAC [1]

11.13.7. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE13, GLP113121, Switch	Overview of Adverse Events		SAC [1]
3.2.	Safety	AE1	Summary of On-therapy Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.3.	Safety	AE1	Summary of Post-therapy Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.4.	Safety	AE3	Summary of Common (>=X%) On-therapy Adverse Events by Overall Frequency	ICH E3	SAC [1]
3.5.	Safety	AE1	Summary On-therapy Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.6.	Safety	AE1	Summary Post-therapy Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.7.	Safety	AE5A	Summary of On-therapy Adverse Events by System Organ Class, Preferred Term and Maximum Intensity	ICH E3	SAC [1]
3.8.	Safety	AE5A	Summary of Post-therapy Adverse Events by System Organ Class, Preferred Term and Maximum Intensity	ICH E3	SAC [1]
3.9.	Safety	AE5A	Summary of On-therapy Drug-Related Adverse Events by System Organ Class, Preferred Term and Maximum Intensity	ICH E3	SAC [1]
3.10.	Safety	AE5A	Summary of Post-therapy Drug-Related Adverse Events by System Organ Class, Preferred Term and Maximum Intensity	ICH E3	SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	Safety	AE15	Summary of Common (>=5%) On-therapy Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [1]
Serious and Other Significant Adverse Events					
3.12.	Safety	AE3	Summary of Pre-Therapy Serious Adverse Events by Preferred Term	GSK CTR	SAC [1]
3.13.	Safety	AE3	Summary of On-Therapy Serious Adverse Events by Preferred Term	GSK CTR	SAC [1]
3.14.	Safety	AE3	Summary of Post-Therapy Serious Adverse Events by Preferred Term	GSK CTR	SAC [1]
3.15.	Safety	AE16	Summary of On-therapy Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [1]
3.16.	Safety	AE1	Summary of On-therapy Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	IDSL	SAC [1]
3.17.	Safety	AE1	Summary of On-therapy Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term		SAC [1]
3.18.	Safety	AE1	Summary of Post-therapy Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term		SAC [1]
Adverse Events of Special Interest					
3.19.	Safety	GLP113121, Switch	Overview of On-therapy Adverse Events of Special Interest		SAC [1]
3.20.	Safety	AE1	Summary of On-therapy Investigator-Reported Cardiovascular Events by SOC and PT		SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.21.	Safety	AE1	Summary of On-therapy Investigator-Reported Atrial Fibrillation / Atrial Flutter by SOC and PT		SAC [1]
3.22.	Safety	New template needed, see DEFEND-1	Summary of Subject-Reported Hypoglycaemic Events by Time Period (3-monthly intervals) and ADA Category		SAC [1]
3.23.	Safety	Switch	Summary of Subject-Reported Hypoglycaemic Events by Plasma Glucose Level		SAC [1]
3.24.	Safety	Switch	Summary of Subject-Reported Daytime and Nocturnal Hypoglycaemic Events by ADA Category		SAC [1]
3.25.	Safety	New	Summary of Subject-Reported Hypoglycaemic Events over Time (2-weekly intervals)	2-weekly intervals	SAC [1]
3.26.	Safety	AE1	Summary of On-therapy Investigator-Reported Pneumonia by SOC and PT		SAC [1]
3.27.	Safety		Summary of On-therapy Investigator-Reported Pancreatitis by SOC and PT		SAC [1]
3.28.	Safety		Summary of On-therapy Investigator-Reported Pancreatitis (Positively Adjudicated by the PAC) by SOC and PT		SAC [1]
3.29.	Safety		Summary of On-therapy Pancreatic Cancer identified from a Customised MedDRA Query by SOC and PT		SAC [1]
3.30.	Safety	AE1	Summary of On-therapy Investigator-Reported Thyroid Events by SOC and PT		SAC [1]
3.31.	Safety	AE1	Summary of On-therapy Gastrointestinal Events by SOC and PT		SAC [1]
3.32.	Safety	GLP113121, Switch	Summary of On-therapy Gastrointestinal Events Over Time		SAC [1]
3.33.	Safety	GLP113121	Summary Characteristics of On-therapy Diarrhoea		SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.34.	Safety	GLP113121	Summary Characteristics of On-therapy Nausea		SAC [1]
3.35.	Safety	GLP113121	Summary Characteristics of On-therapy Vomiting		SAC [1]
3.36.	Safety	AE1	Summary of On-therapy Investigator-Reported Injection Site Reactions by SOC and PT		SAC [1]
3.37.	Safety	GLP113121, Switch	Summary Characteristics of On-therapy Investigator-Reported Injection Site Reactions		SAC [1]
3.38.	Safety		Summary Characteristics of On-therapy Investigator-Reported Injection Site Reactions by Anti-Albiglutide Antibody Status		SAC [1]
3.39.	Safety	AE1	Summary of On-therapy Investigator-Reported Systemic Allergic Reactions by SOC and PT		SAC [1]
3.40.	Safety		Summary of On-therapy Investigator-Reported Renal Impairment by SOC and PT		SAC [1]
3.41.	Safety		Summary of On-therapy Diabetic Ketoacisosis (DKA) identified by a Customised MedDRA Query by SOC and PT		SAC [1]
3.42.	Safety		Summary of On-therapy Appendicitis identified from a Customised MedDRA Query by SOC and PT		SAC [1]
3.43.	Safety		Summary of On-therapy Malignant Neoplams identified from a Standard MedDRA Query by SOC and PT		SAC [1]
3.44.	Safety		Summary of On-therapy Liver Events identified from a Customised MedDRA Query by SOC and PT		SAC[1]
Laboratory: Chemistry					
3.45.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit	ICH E3	SAC [1]
3.46.	Safety	LB17	Summary of Chemistry Shifts from Baseline with Respect to Potential Clinical Importance (PCI) Criteria	ICH E3	SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.47.	Safety	LB1	Summary of Hematology Changes from Baseline by Visit	ICH E3	SAC [1]
3.48.	Safety	LB17	Summary of Hematology Shifts from Baseline with Respect to Potential Clinical Importance (PCI) Criteria	ICH E3	SAC [1]
Laboratory: Urinalysis					
3.49.	Safety	LB1	Summary of Urinalysis Changes from Baseline by Visit	ICH E3	SAC [1]
3.50.	Safety	UR3	Summary of Urinalysis Categorical Results	IDSL	SAC [1]
Laboratory: Hepatobiliary (Liver)					
3.51.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC [1]
3.52.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC [1]
ECG					
3.53.	Safety	EG1, GLP113121, Switch	Summary of ECG Findings by Visit	IDSL	SAC [1]
3.54.	Safety	EG2, per vitals/lab templates	Summary of ECG Changes from Baseline by Visit	IDSL	SAC [1]
3.55.	Safety	per vitals/lab templates	Summary of ECG Shifts from Baseline with Respect to Potential Clinical Importance (PCI) Criteria		SAC [1]
3.56.	Safety	CP_EG11, GLP113121, Switch	Summary of QTcB and QTcF ECG Results by Visit and Category	IDSL	SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.57.	Safety	CP_EG12, GLP113121, Switch	Summary of QTcB and QTcF ECG Changes from Baseline by Visit and Category	IDSL	SAC [1]
Vital Signs					
3.58.	Safety	VS1	Summary of Changes from Baseline in Vital Signs by Visit	ICH E3	SAC [1]
3.59.	Safety	VS7	Summary of Vital Signs Shifts from Baseline with Respect to Potential Clinical Importance (PCI) Criteria	IDSL	SAC [1]
Immunogenicity					
3.60.	Safety	GLP113121	Positive Immunogenicity Results for Anti-Albiglutide Antibody Positive Subjects by Visit		SAC [1]
3.61.	Safety	GLP113121	Positive Immunogenicity Results for Anti-Albiglutide Antibody Positive Subjects by Therapy Phase		SAC [1]
3.62.	Safety	GLP113121	Positive Immunogenicity Results for Anti-Albiglutide Antibody Positive Subjects by Visit, Excluding Subjects with Positive Anti-Albiglutide Antibody at Baseline		SAC [1]

11.13.8. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	New	Plot of Subject-Reported Hypoglycaemic Events by Onset Date Interval	2 weekly intervals	SAC [1]
3.2.	Safety	New	Plot of Mean Number of Subject-Reported Hypoglycaemic Events per Subject by Onset Date Interval	2 weekly intervals	SAC [1]
Laboratory					
3.3.	Safety	LIVER14	Scatter Plot of Maximum Post-Baseline ALT vs. Baseline for ALT	IDSL	SAC [1]
3.4.	Safety	LIVER9	Scatter (eDISH) Plot of Maximum Post-Baseline Total Bilirubin vs. Maximum Post-baseline ALT	IDSL	SAC [1]

11.13.9. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma Concentration data					
4.1.	PK	Study 57–yr 2	Summary of Plasma Concentrations of Albiglutide by Visit		SAC [1]

11.13.10. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma Concentration data					
4.1.	PK	See PK guidance (similar 107085)	Plot of Mean (±SD) Plasma Concentration of Albiglutide by Visit	Separate Linear Scale and Semi-logarithmic scale plots on the same figure	SAC [1]
4.2.	PK	See PK guidance (similar 107085)	Plot of Median Plasma Concentration of Albiglutide by Visit	Separate Linear Scale and Semi-logarithmic scale plots on the same figure	SAC [1]
4.3.	PK	Study 57–yr 2	Scatter Plot of Plasma Concentration of Albiglutide by Visit	Also showing box and whiskers for median and percentiles.	SAC [1]

11.13.11. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Randomised		Subject Disposition		SAC [1]
2.	Screened	ES7	Reasons for Screen Failure	Journal Guidelines	SAC [1]
3.	Safety	ES2	Reasons for Study Withdrawal	ICH E3	SAC [1]
4.	Safety	SD2	Reasons for Study Treatment Discontinuation	ICH E3	SAC [1]
5.	Safety	BL1	Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC [1]
6.	Randomised	TA1	Planned and Actual Treatments	IDSL	SAC [1]
Protocol Deviations					
7.	Safety	DV2	Important Protocol Deviations	ICH E3	SAC [1]
8.	Safety	IE3	Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [1]
Populations Analysed					
9.	Randomised	SP3	Subjects Excluded from Any Population	ICH E3	SAC [1]
Demographic and Baseline Characteristics					
10.	Safety	DM2	Demographic Characteristics	ICH E3	SAC [1]
11.	Safety	DM9	Race	ICH E3	SAC [1]
12.	Safety	SU2	Substance Use		SAC [1]
13.	DEFEND-1 subjects	DM2	Demographic Characteristics (DEFEND-1 subjects)		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Medical History					
14.	Safety	MH2 or Metabolic 1.3	Past/Current Medical Conditions		SAC [1]
15.	Safety		Medical/Surgical Procedure History		SAC [1]
16.	Safety		Family History of Cardiovascular Risk Factors, Pancreatitis and Thyroid Cancer		SAC [1]
Prior and Concomitant Medication					
17.	Safety	CM3	Prior, Concomitant and Post-Therapy Medications	IDSL	SAC [1]
18.	Safety	CM6	Relationship between ATC Level 1, Dictionary Term and Verbatim Text		SAC [1]
Exposure and Treatment Compliance					
19.	Safety	EX3	Exposure Data and Compliance	ICH E3	SAC [1]
20.	Safety		Investigational Product Accountability		SAC [1]
Efficacy					
21.	ITT		C-Peptide AUC [nmol/L] (MMTT)		SAC [1]
22.	ITT		Maximum Stimulated C-Peptide [nmol/L] (MMTT)		SAC [1]
23.	ITT		Plasma Glucagon AUC [NG/L] (MMTT)		SAC [1]
24.	ITT		HbA1c [% and mmol/mol]		SAC [1]
25.	ITT		Responders (Subjects achieving HbA1c $\leq$7.0% and mean daily insulin use <0.5 units/kg/day)		SAC [1]
26.	ITT		Partial Remission Status (Subjects achieving IDAA1c $\leq$ 9.0)		SAC [1]
27.	ITT		Mean Daily Insulin Use [units/kg/day]		SAC [1]
28.	ITT		Subject-Reported Significant Hypoglycaemia Data		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
29.	ITT		7-point Glucose [mmol/L] Profile Data		SAC [1]
30.	ITT		Subject Reported Hypoglycaemic Excursion Data from the 7-point Glucose Profile		SAC [1]
31.	ITT		Subject Reported Hyperglycaemic Excursion Data from the 7-point Glucose Profile		SAC [1]
32.	ITT		72 hour CGM data		SAC [1]
33.	ITT		Time Spent with Plasma Glucose [mmol/L] ≤3.9; >3.9 to ≤10.0; and >10.0 (72h CGM)		SAC [1]
34.	ITT		Body Weight [kg]		SAC [1]
Exploratory Endpoints					
35.	ITT		Urinary C-Peptide Creatinine Ratio (120 minutes) [umol/mol]		SAC [1]
36.	ITT		Anti-GAD, anti-IA-2 and IAA results		SAC [1]
37.	ITT		ADDQoL data		SAC [1]
Adverse Events					
38.	Safety	AE8	Adverse Events	ICH E3	SAC [1]
39.	Safety	AE7	Subject Numbers for Individual Adverse Events	ICH E3	SAC [1]
40.	Safety	AE2	Relationship Between System Organ Class, Preferred Term and Verbatim Text	IDSL	SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
41.	Safety	AE8	Fatal Serious Adverse Events	ICH E3	SAC [1]
42.	Safety	AE8	Non-Fatal Serious Adverse Events	ICH E3	SAC [1]
43.	Safety	AE14	Reasons for Considering as a Serious Adverse Event	ICH E3.	SAC [1]
44.	Safety	AE8	Adverse Events Leading to Permanent Discontinuation of Study Treatment and/or Withdrawal from the Study	ICH E3	SAC [1]
Adverse Events of Special Interest					
45.	Safety	Switch	Investigator-Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina		SAC [1]
46.	Safety	Switch	Investigator-Reported Cardiovascular Events: Congestive Heart Failure		SAC [1]
47.	Safety	Switch	Investigator-Reported Cardiovascular Events: Arrhythmias		SAC [1]
48.	Safety	Switch	Investigator-Reported Cardiovascular Events: Valvulopathy		SAC [1]
49.	Safety	Switch	Investigator-Reported Cardiovascular Events: Pulmonary Hypertension		SAC [1]
50.	Safety	Switch	Investigator-Reported Cardiovascular Events: Cerebrovascular Events Stroke and Transient ischemic attack		SAC [1]
51.	Safety	Switch	Investigator-Reported Cardiovascular Events: Peripheral Arterial Thromboembolism		SAC [1]
52.	Safety	Switch	Investigator-Reported Cardiovascular Events: Deep Vein Thrombosis / Pulmonary Embolism		SAC [1]
53.	Safety	Switch	Investigator-Reported Cardiovascular Events: Revascularisation		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
54.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Atrial Fibrillation / Atrial Flutter		SAC [1]
55.	Safety	Switch	Subject-Reported Hypoglycaemic Data		SAC [1]
56.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Pneumonia		SAC [1]
57.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Pancreatitis		SAC [1]
58.	Safety	LIVER5	Liver Monitoring/Stopping Event Reporting		SAC [1]
59.	Safety	MH2 or Metabolic 1.3	Medical Conditions at Onset of Liver Event for Subjects with Liver Stopping Events		SAC [1]
60.	Safety	SU2	Alcohol Intake at Onset of Liver Event for Subjects with Liver Stopping Events		SAC [1]
61.	Safety	LIVER6	Liver Stopping Event Information for RUCAM Score		SAC [1]
62.	Safety	LIVER7	Liver Biopsy Details		SAC [1]
63.	Safety	LIVER8	Liver Imaging Details		SAC [1]
64.	Safety		Customised MedDRA Query Identified Liver Events		SAC [1]
65.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Thyroid Adverse Events: Thyroid Cancer, Nodules or Goiter Diagnosis		SAC [1]
66.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Injection Site Reactions		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
67.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Systemic Allergic Reactions (Hypersensitivity)		SAC [1]
68.	Safety	Harmony, Switch, GLP113121	Investigator-Reported Renal Impairment		SAC [1]
69.	Safety	Harmony, Switch, GLP113121	Customised MedDRA Query Identified Diabetic Ketoacidosis (DKA)		SAC [1]
70.	Safety	Harmony, Switch, GLP113121	Customised MedDRA Query Identified Appendicitis		SAC [1]
71.	Safety	Harmony, Switch, GLP113121	Customised MedDRA Query Identified Pancreatic Cancer		SAC [1]
72.	Safety	Harmony, Switch, GLP113121	Standard MedDRA Query Identified Malignant Neoplasms		SAC [1]
All Laboratory					
73.	Safety	LB5	All Laboratory Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [1]
74.	Safety	LB14	Laboratory Data with Character Results		SAC [1]
Hepatobiliary (Liver)					
75.	Safety	LIVER13	Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
76.	Safety		All ECG data for Subjects with Any Value of Potential Clinical Importance		SAC [1]
77.	Safety	CP_EG5 / CP_EG6	Abnormal ECG Finding	IDSL	SAC [1]
Vital Signs					
78.	Safety		All Vital Signs for Subjects with Any Value of Potential Clinical Importance		SAC [1]

11.13.12. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
79.	Safety		Anti-Albiglutide Antibody Results		SAC [1]
80.	Safety		Anti-GLP-1 Antibody Results for Anti-Albiglutide Antibody Positive Subjects		SAC [1]
81.	Safety		Anti-HA (Albumin) Antibody Results for Anti-Albiglutide Antibody Positive Subjects		SAC [1]
82.	Safety		Anti-Albiglutide IgE Antibody Results		SAC [1]
Plasma Concentration Data					
83.	PK		Albiglutide Plasma Concentration [ng/mL] data		SAC [1]

11.14. Appendix 14: Example Mock Shells for Data Displays

Example : [Insert Example Reference]
Protocol : [Insert Protocol Number]

Table [Insert Table Number]
[Insert Title]
([Insert Population])