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

Title	:	Reporting and Analysis Plan for Study 200977: Albiglutide + Insulin Glargine Versus Insulin Lispro + Insulin Glargine in the Treatment of Subjects With Type 2 Diabetes Mellitus: The Switch Study
Compound Number	:	GSK716155
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Version Number	:	Final 1.0

Description:

- This reporting and analysis plan describes the statistical analyses that will be conducted for protocol 200977.
- This RAP is intended to describe the planned efficacy (primary, secondary and exploratory) and safety analyses required for the study.
- This document will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) Deliverable.

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TABLE OF CONTENTS

PAGE

1. REPORTING AND ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the Reporting and Analysis Plan (RAP)
Purpose	• This study will evaluate the efficacy and safety of once-weekly albiglutide administered in combination with basal insulin as a replacement for bolus insulin in subjects with type 2 diabetes mellitus (T2DM) who are currently managed with a basal-bolus insulin regimen but who are not achieving glycemic treatment goals. It is expected that subjects switched to albiglutide plus basal insulin (with discontinuation of bolus insulin therapy) compared with those intensifying basal-bolus insulin therapy will be able to maintain glycemic control with less hypoglycemia and less weight gain, while also demonstrating a reduced total daily insulin requirement and reduced number of weekly injections (e.g., 28 injections per week [7 basal insulin and up to 21 bolus insulin injections] in basal-bolus-treated subjects compared with potentially 8 injections per week [1 weekly albiglutide injection and 7 basal injections] in subjects switching to basal insulin plus albiglutide). Data from this study will support the concept that albiglutide is a potential alternative to bolus insulin that will simplify insulin therapy in subjects with T2DM that do not reach adequate control with basal-bolus therapy.
Protocol	• This RAP is based on the protocol amendment 3 (Dated: 24-SEP-2015) of study GSK200977 (GSK Document No. : 2013N187697_02) and eCRF Version 6.01.
Primary Objective	• To evaluate the glycemic effectiveness of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM receiving basal-bolus insulin therapy.
Primary Endpoint	• Change from Baseline in HbA_{1c} at Week 26.
Study Design	• This Phase IIIb, randomized, open-label, parallel-group, active-control, multicenter, treat-to-target study of 26 weeks' treatment duration will evaluate the efficacy and safety of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM. • The study will comprise 4 study periods: Screening (2 weeks), Standardization (4 weeks), Treatment (26 weeks), and Post-treatment Follow-up (4 weeks). The total duration of a subject's participation will be approximately 36 weeks. Subjects will have 10 study center visits and approximately 18 telephone calls to monitor insulin titration. • After the Standardization Period, subjects meeting additional criteria for randomization will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus 65 years), and current background metformin (metformin use versus no metformin use). Approximately 794 subjects will be randomly assigned to albiglutide + insulin glargine (with or without metformin) or intensification of insulin glargine + insulin lispro (with or without metformin) in a 1:1 ratio.
Planned	• Final Analysis: After all subjects have completed the planned 26 weeks of

Overview	Key Elements of the Reporting and Analysis Plan (RAP)
Analyses	randomized study treatment and the subsequent follow-up phase, the final analysis for the clinical study report will be performed. At this time, the database will be frozen.
Analysis Populations	• Full Analysis (FA) Population • Per-Protocol (PP) population • Safety Population
Hypothesis	• The primary hypothesis to be tested is that albiglutide plus insulin glargine (with or without metformin) will provide glycemic control (as measured by HbA_{1c} change from Baseline) noninferior to insulin lispro plus insulin glargine (with or without metformin) after 26 weeks of treatment in subjects with T2DM inadequately controlled on their current regimen of basal-bolus insulin therapy.
Primary Analyses	• The primary endpoint is the change from Baseline in HbA_{1c} at Week 26. The primary analysis of the primary endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the FA Population. The MMRM will only include non-missing observations without imputation.
Secondary Analyses	• Categorical endpoints will be analyzed using CMH test and logistic regression adjusting for baseline HbA_{1c} category, age category, region and current use of metformin. Continuous endpoints will be analyzed using a MMRM model for the FA population. Time to event data will be analyzed using a log-rank test with Kaplan-Meier method.
Exploratory Analyses	• Exploratory endpoints will be analysed in a similar manner as described above for the secondary endpoints.
Safety Analyses	• Adverse events, adverse events of special interest, hypoglycemic events, clinical laboratory tests, vital signs and ECG findings will be presented by treatment groups.

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 amendment 3 (Dated: 24-SEP-2015) are outlined as follows:

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Supportive secondary endpoint: Total daily insulin dose (24-hour total international units [IU] and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, and 18 visits.	• Use prescribed total daily insulin dose and prescribed total daily units/kg body weight for analysis. Do not use the actual dose taken or the doses over the 3 days preceding the visits.	• The prescribed dose reflects the investigator's assessment of what would be required to maintain or achieve glycemic control. The 'over the 3 days preceding the Baseline/Randomization and Week 4, 10, and 18 visits' text is a carryover from earlier protocol.

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the glycemic effectiveness of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM receiving basal-bolus insulin therapy	• Change from Baseline in HbA_{1c} at Week 26
Key Secondary	
• To determine the proportion of subjects treated with once-weekly albiglutide that are able to replace prandial insulin without the need for re-introduction of insulin lispro	• Proportion of subjects treated with once-weekly albiglutide that are able to discontinue insulin lispro at Week 4 and do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26
• To demonstrate a significant difference in the frequency of hypoglycemic events between treatment groups	• Percentage of subjects with severe or documented symptomatic hypoglycemia through Week 26
• To demonstrate a significant difference in body weight between treatment groups	• Change from Baseline in body weight at Week 26 and over time
• To demonstrate a significant	• Prescribed total daily insulin dose at Week 26

Objectives	Endpoints
reduction in total daily dose of insulin between treatment groups	
Supportive Secondary	

• To assess additional glycemic parameters, achievement of HbA_{1c} treatment goals, body weight, and total daily insulin dose	• Additional glycemic parameters:
	  • HbA_{1c} change from Baseline over time
	  • FPG change from Baseline at Week 26 and over time
	• Achievement of HbA_{1c} treatment goals:
	  • Proportion of subjects achieving a HbA_{1c} <7.0% at Week 26 and over time
	  • Proportion of subjects achieving a HbA_{1c} <6.5% at Week 26 and over time
	• Incidence and time to meeting prespecified criteria for severe, persistent hyperglycemia through Week 26
	• Additional assessments of daily insulin doses:
	  • Prescribed total daily insulin dose (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, and 18 visits
	  • Prescribed total daily basal insulin dose (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, 18, and 26 visits
	  • Prescribed total daily bolus insulin dose (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, 18, and 26 visits
	• Total number of weekly insulin injections (7 days) to achieve glycemic control to achieve glycemic control at Baseline/Randomization and Week 4, 10, 18, and 26
	• Composite endpoints (after 26 weeks of treatment):
	  • Percentage of subjects achieving HbA_{1c} <7.0% without weight gain
	  • Percentage of subjects achieving HbA_{1c} <7.0% without severe or documented symptomatic hypoglycemia
	  • Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without severe or documented Hypoglycemia

• To evaluate the safety and tolerability of the 2 treatment groups	• Adverse events (AEs) and serious AEs (SAEs), including AEs and SAEs leading to discontinuation of randomized study medication • Other AEs of special interest (for example, cardiovascular [CV] events, GI events, injection site

Objectives	Endpoints

	reactions, potential systemic allergic reactions, pancreatitis, pancreatic cancer, medullary thyroid cancer, malignant neoplasms following treatment with insulin, diabetic retinopathy events, appendicitis, liver events, pneumonia, and atrial fibrillation/flutter)
	• Assessments of hypoglycemia:
	  • Percentage and number of events of hypoglycemia with confirmed home blood glucose monitoring and/or third-party intervention through Week 26 (i.e., severe, documented symptomatic, and asymptomatic hypoglycemic events, see Protocol Section 6.3.1) in 3-month intervals (i.e., from Baseline/Randomization to Week 12, >Week 12 to Week 26)
	  • Incidence of hypoglycemic events (in total and by each category as defined by the American Diabetes Association criteria)
	  • Incidence of daytime hypoglycemia (in total and by category), defined as hypoglycemic events with an onset between 06:00 hours and 00:00 hours (inclusive), and nocturnal hypoglycemia (in total and by category), defined as hypoglycemic events with an onset between 00:01 hours and 05:59 hours (inclusive)
	  • Incidence of hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L), regardless of symptoms
	• Assessment of clinical laboratory tests (hematology, clinical chemistry, urinalysis, β-human chorionic gonadotropin [β-HCG], lipid panel)
	• Assessment of vital sign measurements (Note: Weight is assessed as part of efficacy) and 12-lead electrocardiogram (ECG) findings

Exploratory	

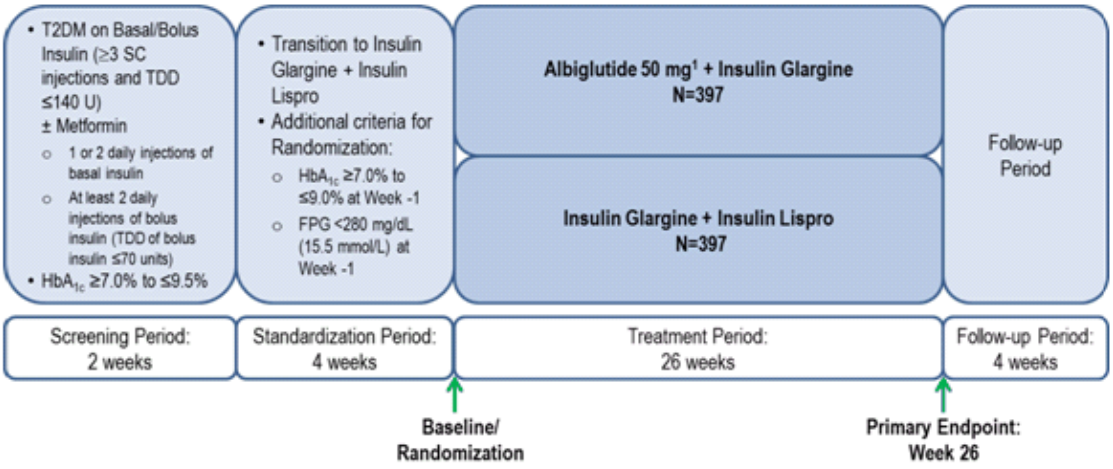
• To compare the effects between the 2 treatment groups on patient-reported outcomes to diabetes medication and to further assess glycemic parameter, weight, and composite endpoints	• Patient-reported outcomes to diabetes medication at Baseline/Randomization, Week 10, and Week 26:
	  • Treatment-related impact measure for diabetes (TRIM-Diabetes) questionnaire
	  • Hypoglycemia fear survey-II (HFS-II) worry subscale
	• Additional glycemic parameter, weight, and composite endpoints:
	  • HbA_{1c} change from Baseline at Week 26 by baseline FPG tertiles
	  • FPG change from Baseline at Week 26 by

Objectives	Endpoints
	baseline FPG tertiles • 24-hour glucose profile: 8-point self-monitored blood glucose (SMBG) profile at Baseline/Randomization, Week 10, and Week 26 (before and 120 minutes after the 3 main meals, at bedtime, and at 2 AM) • Mean daily blood glucose based on the 8-point SMBG profile at Baseline/Randomization, Week 10, and Week 26 • Number (and percentage) of subjects with <=1 kg weight gain at Week 26 • Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L) regardless of symptoms at Week 26 • Proportion of subjects treated with once-weekly albiglutide that are able to totally replace or decrease prandial insulin without worsening HbA_{1c} control (worsening defined as >0.3% increase in HbA_{1c} compared with baseline HbA_{1c}) at Week 26
• Analysis of genetic sampling may also be performed	• Genetic sampling
• Analysis of novel biomarkers may also be performed	• Novel biomarker analysis may be performed; a decision on whether to analyze novel biomarker samples may be made after review of efficacy and safety endpoints at the end of the study or other emerging information that may become available during the study

2.3. Study Design

2.3.1. Overview of Study Design and Key Features

Overview of Study Design and Key Features



SC = subcutaneous; T2DM = type 2 diabetes mellitus; TDD = total daily dose.
Note: Subjects on metformin will continue on the same dose throughout the study, except if the subject's estimated glomerular filtration rate, calculated according to the Modification of Diet in Renal Disease formula, decreases during the study to a level where metformin is contraindicated according to its label (as appropriate for each participating country), in which case metformin is to be stopped.
1. At Baseline/Randomization, albiglutide will be started at 30 mg once weekly with uptitration to albiglutide 50 mg once weekly at Week 4. Subjects randomly assigned to this treatment group will reduce insulin lispro by 50% at Baseline/Randomization, followed by complete (100%) discontinuation of insulin lispro at Week 4.

Design Features	• Randomized, open-label, parallel-group, active-control, multicenter study of 26 weeks' treatment duration
Dosing	• Albiglutide will be started at 30 mg once weekly with uptitration to Albiglutide 50 mg once weekly at Week 4. For insulin glargine and insulin lispro, see Protocol Section 5.
Treatment Assignment	• After the Standardization Period, approximately 794 subjects meeting additional criteria for randomization will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and current use of background metformin (metformin use versus no metformin use) and randomly assigned to 1 of the 2 treatment groups in a 1:1 ratio: albiglutide + insulin glargine (± metformin) or insulin lispro + insulin glargine (± metformin).
Interim Analysis	• No interim analysis is planned for this study.

2.3.2. Study Design

This Phase IIIb, randomized, open-label, parallel-group, active-control, multicenter study of 26 weeks' treatment duration will evaluate the efficacy and safety of once weekly albiglutide plus insulin glargine compared with insulin lispro plus insulin glargine in subjects with T2DM failing to achieve adequate glycemic control with basal-bolus therapy (± metformin).

The study will comprise 4 study periods: Screening (2 weeks), Standardization (4 weeks), Treatment (26 weeks), and Post-treatment Follow-up (4 weeks). The total duration of a subject's participation will be approximately 36 weeks.

After Screening, eligible subjects will enter a 4-week Standardization Period to transition from their current basal-bolus therapy to insulin glargine/insulin lispro. Subjects already on insulin glargine/insulin lispro will also enter the Standardization Period.

After the 4-week Standardization Period, eligible subjects will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and current use of metformin (metformin use versus no metformin use). Approximately 794 subjects (Appendix 12: Sample Size Considerations) will be randomized in a 1:1 ratio such that

- Approximately 397 subjects are randomly assigned to albiglutide + insulin glargine (± metformin)
- Approximately 397 subjects are randomly assigned to insulin lispro + insulin glargine (± metformin)

Following randomization, albiglutide subjects will initiate treatment with once-weekly subcutaneous injections of albiglutide 30 mg (with forced uptitration to albiglutide 50 mg at Week 4).

During the treatment period, the study will allow individualization of the insulin dose in both treatment arms (i.e., insulin glargine in the albiglutide arm and both insulin glargine and insulin lispro in the basal-bolus arm), with a treat-to-target approach and a titration regimen based on FPG.

Subjects taking metformin as background antidiabetic medication will remain on their current dose for the duration of their participation in the study, unless a decline in kidney function results in a contraindication for metformin use.

The total duration of a subject's participation will be approximately 36 weeks (approximately 2 weeks of Screening, 4 weeks of Standardization, a 26-week Treatment Period, and 4 weeks of Post-treatment Follow-up). Subjects who discontinue active participation in the study will no longer receive the randomized study medication. Immediately upon discontinuation from active participation in this study, these subjects should complete the early withdrawal assessments (i.e., safety and laboratory assessments) and return 4 weeks later for the follow-up assessments.

Subject completion is defined as completion of all periods of the study up to and including the follow-up visit. For the primary analysis, subject completion is defined as completion of all periods of the study up to and including the treatment period.

2.4. Statistical Hypotheses

The primary hypothesis to be tested is that albiglutide plus insulin glargine (with or without metformin) will provide glycemic control (as measured by HbA_{1c} change from Baseline) noninferior to insulin lispro plus insulin glargine (with or without metformin) after 26 weeks of treatment in subjects with T2DM inadequately controlled on their current regimen of basal-bolus insulin therapy. If the null hypothesis of albiglutide inferiority is rejected, a test of superiority will be applied.

- The null hypothesis is that the difference in the mean change from Baseline to Week 26 in HbA_{1c} between albiglutide and insulin lispro is greater than the non-inferiority margin of 0.3%.
- The alternative hypothesis is that the difference in the mean change from Baseline to Week 26 in HbA_{1c} between albiglutide and insulin lispro is less than or equal to the non-inferiority margin of 0.3%.

The hull hypothesis will be tested based on the upper bound of 1-sided 97.5% confidence interval (equivalently, the upper bound of a 2-sided 95% confidence interval) of the least squares mean of the treatment difference estimated from a MMRM model. The MMRM model will include HbA_{1c} change from Baseline as the dependent variable, treatment, region, age category, current use of metformin, visit week, treatment-by-week interaction, and baseline HbA_{1c}-by-week interaction as the fixed effects, and baseline HbA_{1c} as a continuous covariate. Subject will be included in the model as a random effect. If the upper bound of 1-sided 97.5% confidence interval is less than or equal to 0.3%, non-inferiority will be concluded. If non-inferiority is established, a superiority test will be performed and the upper bound of 1-sided 97.5% confidence interval will be compared to 0. If it is less than 0, superiority will be claimed. This superiority test with respect to HbA1c will be performed after testing the key secondary hypotheses.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.

3.2. Final Analyses

After all subjects have completed the planned 26 weeks of randomized study treatment or withdrawn from the study and the subsequent follow-up phase, the final analysis for the clinical study report will be conducted. At this time, the database will be frozen after all required database cleaning activities have been completed.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Full Analysis (FA)	• Comprise of all subjects randomly assigned to treatment. • Randomly assigned subjects who do not receive any study treatment will also be included. • The subjects in the FA Population will be analyzed according to randomized treatment.	• Study Population • Efficacy
Per-Protocol (PP)	• Comprise of all randomized (FA Population) subjects who complete study procedures through Week 26 or beyond. • The subjects in the PP Population will be analyzed according to randomized treatment.	• Supportive Efficacy Analysis
Safety	• Include all subjects who receive at least 1 dose of randomized study medication. • The subjects in the Safety Population will be analyzed according to the treatment received.	• Safety • Study Population

NOTES :

- Please refer to Appendix 14: List of Data Displays which details the population to be used for each displays being generated.

4.1. Deviations from Assigned Treatment

If subjects do not take treatment according to their randomization, the assignment of treatment for summary and analysis will both depend on the extent of the violation and the type of data being analyzed.

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

4.2. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to freezing the database to ensure all protocol deviations are identified and documented.
  - This dataset will be the basis for the summary of significant deviations and listing of all protocol deviations.

- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

The primary analysis in this study is comparison between the treatment groups on the primary efficacy endpoint change from baseline in HbA_{1c} with MMRM, where missing HbA1c values are assumed to be missing at random. Missing data handling and sensitivity analysis for the primary endpoint can be found in Appendix 6: Premature Withdrawals & Handling of Missing Data.

In the conduct of the study, specific measures will be put in place to prevent and minimize missing data due to treatment withdrawals, noncompliance, etc. Upon study completion, the characteristics (frequency, causes) of the missing data, especially as related to the key efficacy endpoints, will be examined to inform the sensitivity analysis and imputation methods concerning missing data.

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

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Management Plan and Definitions for Per-Protocol Population
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Treatment Periods
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Multicenter Studies and Definition of Geographic Region for Statistical Analyses
11.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
11.10	Appendix 10: Multiple Comparisons & Multiplicity
11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses
11.12	Appendix 12: Sample Size Considerations
11.13	Appendix 13: Abbreviations and Trademarks
11.14	Appendix 14: List of Data Displays

5.1. Multiple Comparisons and Multiplicity

A multiple comparisons adjustment strategy will be implemented for the multiple inferential tests among the primary and key secondary endpoints to preserve the family-wise Type I error rate of 0.05. Testing on other efficacy endpoints will be considered

exploratory and no multiplicity adjustment will be applied. Details are provided in Appendix 10: Multiple Comparisons and Multiplicity.

5.2. Withdrawal

Subjects withdrawn after not achieving a predefined threshold for glycemic control (confirmed FPG ≤270 mg/dL [15.0 mmol/L] at least 8 weeks after randomization) may be considered for study withdrawal. Subjects withdrawn for this reason will be considered to have completed the efficacy assessments for the primary analysis at the time of the assessment that triggers withdrawal. Per the protocol, insulin lispro may be re-introduced after Week 8 for subjects in the albiglutide treatment group, following a standardized, stepwise approach. Efficacy and safety assessments after the re-introduction of lispro will be included in the statistical analysis as is, without special handling.

5.3. Geographic Region

Clinical sites will be clustered by geographic region since the number of subjects per clinical site is expected to be rather small. Geographic regions will be defined based on geographic proximity, similarity of medical practice in diabetes, and number of subjects per region. Subjects per region will be constrained such that the region with the largest sample size is no more than 3 times that of the region with the smallest sample size. The classification of region will be determined prior to the database lock and initiation of the final analyses, and documented in Appendix 8.

5.4. Baseline and Study Day

In general, the baseline value for each variable will be defined as the last measurement collected prior to the first dose of randomized study medication.

Study day will be defined as the number of days from the first dose of randomized study medication. The date when a subject receives the first dose of randomized study medication is defined as Day 1. For events after the first dose date, study day is calculated as the difference in days between the first dose date and the date of interest, plus 1 day. For events that occur before the first dose date, study day is calculated as the difference in days between the first dose date and the date of interest. Thus, the day before first dose date is defined as Day -1.

5.5. Analysis Visit Window and Therapy Periods

For all safety and efficacy parameters to be summarized or analyzed by visit, data records will be slotted to one of the protocol specified visits using the algorithm defined in Appendix 3.

For classifying AEs (including hypoglycemic events), the therapy periods will be defined as pre-therapy, on-therapy and post-therapy. Albiglutide has a half-life of about 5 days in human body. Five times the half-life of a drug starting from the last dose of treatment is considered as the elimination period after which the drug has practically been eliminated from the system. Last dose date plus a period of 5 times of half-life of albiglutide, which

is within 25 days after the date of last dose, is defined as on-therapy window for subjects in the albiglutide arm. An AE is defined as on-therapy AE if the onset date is on or after the start date of randomized study medication and within last dose date plus 25 days in the albiglutide arm or within the last dose date in the lispro arm. For other safety parameters that are assessed prior to administration of randomized study medication on dosing days, the assessment date is used to determine the therapy periods. Details on the therapy periods of AEs and other safety parameters are provided in Appendix 4.

5.6. Multiple Evaluations

After all the records have been slotted based on therapy period and study day, if there are multiple valid records for an assessment within an assigned analysis visit, only one of these records will be used for summary statistics and analyses. The record to be used is determined using the following hierarchy (in decreasing order of priority):

- the record closest to the target visit day
- the record with an original nominal visit that matches the analysis visit
- the record earliest in time for postbaseline assessments; for baseline, it is the record latest in time

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the population specified in Section 4.

Table 2 provides an overview of the planned study population analyses with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Format		
	Figure	Table	Listing
Randomization			
Randomization			Y
Subject Disposition			
Subject Disposition		Y	Y
Reasons for Screening Failures and Standardization Failures		Y	Y
Reasons for Withdrawal from Study		Y	Y
Reasons for Discontinuing Study Treatment		Y	Y
Protocol Deviations		Y	Y
Deviations Leading to Exclusions from PP Population		Y	Y
Inclusion and Exclusion Criteria Deviations		Y	Y
Demography			
Demographics and Baseline Characteristics		Y	Y
Race & Racial Combinations		Y	Y
Substance use		Y	Y
Study Populations		Y	Y
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)		Y	Y
Concomitant Medication		Y	Y
Exposure and Treatment Compliance			
Treatment Compliance		Y	Y
Exposure to Study Drug		Y	Y
Dose Titration			
Dose Titration			Y

Note: additional tables, listings and figures will be provided in Appendix 14: List of Data Displays.

6.2. Disposition of Subjects

The number of subjects who were randomized and the number of subjects within each population (Full Analysis, Safety, Per- Protocol) will be summarized for each treatment group. A summary of subjects randomized by geographic region, country, and site will also be provided by treatment group.

The numbers and percentages of subjects who completed the study, discontinued the study, and discontinued the study treatment, along with reasons for discontinuation, will be summarized by treatment group.

A subject status by visit summary will be provided.

Subject disposition data will be listed as well. All disposition summaries will be based on all randomized subjects (i.e., FA Population).

6.3. Protocol Deviations

As described in Section 4.2, subjects who fail to meet any of the inclusion/exclusion criteria will be tabulated and listed by treatment group for FA Population. This will be based on data recorded on the inclusion/exclusion page of the eCRF. A separate listing or summary (if applicable) of significant protocol deviations (described in Section 4.2) will be generated.

6.4. Demographic and Baseline Characteristics

Continuous variables such as age, body mass index, weight, and height will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables including age group (<65, ≥65 years), sex, race, ethnicity, baseline HbA_{1c} category (<8%, ≥8%), and current metformin use (yes, no) will be summarized using numbers and percentages. Summaries will be presented by treatment group using the FA Population and Safety Population.

Summary of substance (alcohol and tobacco) use will be provided, as well as a by-subject listing of data on alcohol and tobacco use. All summaries will be performed using the FA Population.

6.5. Exposure to Study Drug

Descriptive statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum for the duration of study drug exposure to the treatment received will be presented by treatment group for the Safety Population. The duration of study drug exposure is defined as date of last dose of randomized study drug - date of first dose of randomized study drug + 1. The total person time on treatment (in years) as defined in Appendix 5 will also be displayed for each treatment group.

Additionally, the prescribed total daily dose of insulin glargine and insulin lispro will be tabulated by visit.

A by-subject listing of study drug administration will also be presented.

6.6. Treatment Compliance

Investigational product accountability will be done for albiglutide at each study visit after the baseline visit through the end-of-treatment visit (Visit 9, Week 26).

Albiglutide treatment compliance will be calculated as total number of doses administered divided by total number of doses expected based on the last dose date at the end of active treatment period. Total number of albiglutide administered during the treatment period will be computed as the number of expected dose minus the number of missed dose. For the number of expected dose, if subject completes the treatment, it will be 26. If subject doesn't complete the treatment, the number of expected dose will be equal to the number of weeks between treatment start date and treatment end date. The number of missed dose information, treatment start and end date are captured on the albiglutide administration CRF page. Treatment compliance will be summarized for all subjects, as well as for subjects who discontinue treatment early and subjects who complete active treatment. Summary statistics for treatment compliance percentages, as well as the number and percentage of subjects who are <80% and ≥80%compliant will be reported for the Safety Population. Individual subject compliance information will also be listed.

Treatment compliance of subjects for insulin glargine and insulin lispro will be assessed by the investigator at each visit and reported on the eCRFs. At each visit on or after baseline, the investigator will answer "yes/no" to the question of "Do you believe the subject has been compliant with their insulin regimen at least 80% of the time". If the investigator answered "yes" for all the postbaseline visits for treatment compliance assessment (Week 4, 10, 18, and 26), the subject will be considered as being >=80% compliant to the treatment during the entire study period. For subjects who discontinued the study early, the same rule will apply and the assessment of overall compliance will be based on the data from the completed visits. The number and percentage of subjects in each compliance category will be summarized overall and by study visit for the safety population. Individual subject compliance information will be listed.

Acceptable overall compliance for IP (albiglutide) and other study treatments (insulin glargine and insulin lispro) in this study will be ≥80%.

6.7. Dose Titration and Insulin Lispro Re-introduction

The albiglutide dose in this study will start at 30 mg weekly and be titrated to 50 mg weekly at Week 4.

Both treatment arms will follow the same insulin glargine titration algorithm during the Standardization and Treatment Periods (see Table 3 of the Protocol).

Both treatment arms will follow the same insulin lispro titration algorithm during the standardization period. At randomization, the start of the treatment period, the insulin lispro titration algorithm will be individualized for each treatment arm (see Table 4 of the protocol).

Insulin lispro may be re-introduced after Week 8 for subjects in the albiglutide treatment group. The number of subjects for whom insulin lispro was re-introduced will be summarized. For these subjects, the re-introduced insulin lispro will be characterized in terms of the number of injections and the total dose over time. The dosing guidance for albiglutide, insulin lispro, insulin glargine, and metformin treatment can be found in Table 2 of the Protocol.

Individual dose titration information and insulin lispro re-introduction will be listed for the safety population.

For lispro re-introduction through Week 26, it will include lispro re-introduced up to Week 25 and not include lispro prescribed at Week 26. This is due to that the last albiglutide injection is given at Week 25 for subjects in albiglutide arm and at Week 26 lispro may be prescribed as per standard of care.

6.8. Medications

Any prior and concomitant medication used during the study will be recorded and coded using GSKDRUG dictionary, which will be updated whenever available throughout the life of the study. Summary of all medications by treatment group and preferred term will be provided in relation to treatment phase (prior medication, concomitant medication, or post-therapy medication). Prior medications are those started and stopped before the first dose of randomized study drug. Concomitant medications are those taken at any time on or after the day of the first dose of randomized study drug and within last dose date plus 25 days in the albiglutide arm or within the last dose date in the lispro arm, including those medications that started prior to randomization and continued into the treatment period. Post-therapy medications are those taken after last dose date plus 25 days in the albiglutide arm or after the last dose date in the lispro arm.

For this study, insulin glargine, insulin lispro and any other anti-hyperglycemic medications will be recorded through screening period on the concomitant medications eCRF pages. Once subjects enter Visit 2 (Standardization Week -4 visit), the prescribed dose for insulin glargine and for insulin lispro are captured in the Insulin Surveillance eCRF page.

All prior and concomitant medications will be listed using generic and verbatim terms. All summaries will be performed using the safety population.

6.9. Medical History

Subject data listings and summary tables will be provided for the following current and/or past conditions:

- cardiovascular medical history
- diabetes history
- medical/surgical procedure history
- gastrointestinal (GI) medical history

- nephropathy (including microalbuminuria) and kidney injury history
- diabetic retinopathy history
- cancer history
- pneumonia medical history
- skin medical conditions
- thyroid history, thyroid cancer history
- history benign thyroid conditions
- thyroid cancer family history
- pancreatitis family history
- pancreatic cancer family history
- other medical history

The number and percentage of subjects with current and/or past cardiovascular medical history will be reported by treatment group. Also, the number and percentage of subjects with current and/or past diabetes history will be tabulated by treatment group. A summary of duration of diabetes disease history in years will be provided. The duration of diabetes disease history is calculated as the years lapsed between screening visit date and T2DM diagnosis date.

The number and percentages of subjects with current and/or past medical/surgical procedure history, gastrointestinal (GI) medical history, nephropathy (including microalbuminuria) and kidney injury history, diabetic retinopathy history, cancer history, pneumonia medical history, skin medical conditions, thyroid history, thyroid cancer history, history benign thyroid conditions, thyroid cancer family history, pancreatitis family history, pancreatic cancer family history and other medical history will be presented in a similar manner as described for cardiovascular medical history.

In addition, by subject listings of medical and family history status and all the medical conditions listed above will be provided.

All summaries will be performed using the safety population. In the case of scarce data for a medical history and summary is not necessary, only a listing will be provided.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the FA population, unless otherwise specified.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Efficacy Analyses

	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
HbA_{1c}	Y			Y	Y		Y	Y	Y		Y	Y		Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Following review of the data, additional analyses may be conducted to further support the evaluation and interpretation of the data.

7.1.1.1. Primary Analysis on Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in HbA_{1c} at Week 26. The primary analysis of the primary efficacy endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the FA population using all available data from analysis visits. Missing data will not be imputed.

The model will include HbA_{1c} change from Baseline as the dependent variable; treatment, region (defined in Appendix 8: Multicenter Studies and Definition of Geographic Region for Statistical Analysis), age category, current metformin use, visit week, treatment-by-week interaction, and baseline HbA_{1c}-by-week interaction as fixed effects; baseline HbA_{1c} as a continuous covariate; and subject as a random effect (Model 1). Treatment effects estimates (and associated hypothesis tests) of albiglutide will be evaluated within this MMRM model as least squares means contrasts relative to insulin lispro. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion (AIC). The MIXED procedure in SAS will be used to implement the MMRM analysis. The least squares means (and standard errors) of HbA_{1c} at each study visit and least squares means (and standard errors) of change from Baseline in HbA_{1c} at each postbaseline study visit will be presented. The least squares mean and the associated 1-sided 97.5% confidence interval of the treatment difference in change from Baseline in HbA_{1c} at each postbaseline study visit will be reported. In addition, the observed HbA_{1c} and change from Baseline HbA_{1c}

will be summarized descriptively. The least squares means (and standard errors) of change from Baseline HbA_{1c} will be plotted by treatment group.

The null hypothesis will be tested based on the 1-sided 97.5% confidence interval of the least squares mean of the treatment difference at Week 26 estimated from the MMRM model. If the upper bound of the confidence interval is less than or equal to 0.3%, non-inferiority will be concluded. If non-inferiority is established, key secondary endpoints will be tested as described in Appendix 11.10.

7.1.1.2. Supportive Analyses on Primary Efficacy Endpoint

The MMRM analysis above assumes that there are no qualitative interactions of treatment with the other terms in the model. For the primary endpoint only, the treatment-by-baseline HbA_{1c}, treatment-by-region, treatment-by-age category, and treatment-by-current metformin use interactions will be investigated individually at a significance level of 0.10. Absence of a significant treatment-by-variable qualitative interaction at the 0.10 level will be interpreted as supportive of the use of the main-effects model to evaluate the treatment efficacy hypotheses. When examining the interaction between the continuous variable HbA_{1c} and treatment, the baseline HbA_{1c} category will be used.

The primary endpoint will also be analyzed using Model 1 in the PP population as supportive analysis.

7.1.1.3. Analyses on Primary Efficacy Endpoint by Subgroups

The primary endpoint, HbA_{1c} change from Baseline at Week 26, will also be examined by the subgroups of a number of variables, such as baseline HbA_{1c} category, gender, race, ethnicity, age category, baseline BMI category, region, duration of diabetes category and current use of metformin (see Appendix 9), using a MMRM model that is similar to the model for the primary analysis but also includes the subgroup-variable-by-treatment-by-visit week interaction term (as well as subgroup-variable-by-treatment and subgroup-variable-by-visit week). The adjusted mean difference and confidence interval for each level of the subgroup will be estimated from the MMRM model and the p-values for the treatment by subgroup interactions will be reported.

7.1.1.4. Sensitivity Analysis

Sensitivity analyses will be performed for the primary efficacy endpoint to assess the robustness of the primary efficacy analysis results with respect to departures from the assumption that missing primary endpoint data are missing at random. Detailed methodology is provided in Appendix 6.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Change from Baseline in HbA_{1c} at Week 26
Model Specification
• Change from Baseline in HbA_{1c} = Baseline HbA_{1c} + Treatment + Region + Age Category + Current Use of Metformin + Visit Week + Treatment-by-Visit Interaction + Baseline HbA_{1c}-by-Visit Week Interaction (**Model 1**)
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• The least squares mean of the treatment difference at Week 26 estimated from the MMRM model and its 1-sided 97.5% confidence interval • Descriptive statistics for the observed HbA_{1c} and change from Baseline HbA_{1c} • Plot of the least squares means (and standard errors) of change from Baseline HbA_{1c} by treatment group • Refer to Appendix 14: List of Data Displays

Supportive Statistical Analysis
• The generalizability of the treatment effect will be evaluated within a supportive MMRM model that adds terms for treatment-by-variable interaction. The variables include baseline HbA_{1c}, region, age category, and current use of metformin. • The primary endpoint will also be analyzed using Model 1 above in the Per-Protocol Population
Model Specification
• Change from Baseline in HbA_{1c} = Baseline HbA_{1c} + Treatment + Region + Age Category + Current Use of Metformin + Visit Week + Treatment-by-Visit Interaction + Baseline HbA_{1c}-by-Visit Week Interaction + Treatment-by-Variable + Visit Week–by-Variable + Treatment-by-Visit Week-by-Variable. • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses for SAS code

By-Subgroup Statistical Analysis
• The subgroup analyses will be performed using MMRM models. The subgroups include baseline HbA_{1c} category, gender, race, ethnicity, age category, baseline BMI category, region, duration of diabetes category and current use of metformin. • Refer to Appendix 9: Examination of Covariates, Subgroups & Other Strata.
Model Specification
• Change from Baseline in HbA_{1c} = Baseline HbA_{1c} + Treatment + Region + Age Category + Current Use of Metformin + Visit Week + Treatment-by-Visit Interaction + Baseline HbA_{1c}-by-Visit Week Interaction+ Treatment-by-Visit Week-by-Variable + Treatment-by-Variable + Visit Week–by-Variable. • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses for SAS code

Sensitivity Statistical Analysis with Respect to Missing Data MAR Assumption
• Refer to Appendix 6, Section 11.6.3: Sensitivity Analysis on the Primary Efficacy Endpoint

8. SECONDARY AND EXPLORATORY STATISTICAL ANALYSES

8.1. Secondary Efficacy Analyses

8.1.1. Overview of Planned Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the Full Analysis (FA) population, unless otherwise specified.

Table 4 provides an overview of the planned secondary efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Secondary Efficacy Analyses

	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Key Secondary Endpoints							
Proportion of subjects treated with once-weekly albiglutide that are able to discontinue insulin lispro at Week 4 and do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26	Y			Y			Y
Percentage of subjects with severe or documented symptomatic hypoglycemia through Week 26	Y			Y			Y
Change from Baseline in body weight at Week 26 and over time	Y	Y		Y	Y		Y
Prescribed total daily insulin dose at Week 26	Y	Y		Y	Y		Y
Supportive Secondary Endpoints							
HbA_{1c} change from Baseline over time	Y	Y		Y	Y		
FPG change from Baseline at Week 26 and over time	Y	Y		Y	Y		Y
Proportion of subjects achieving a HbA_{1c} <7.0% at Week 26 and over time	Y			Y			
Proportion of subjects achieving a HbA_{1c} <6.5% at Week 26 and over time	Y			Y			
Incidence and time to meeting prespecified criteria for severe, persistent hyperglycemia at Week 26	Y	Y		Y			Y
Prescribed total daily insulin dose (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, and 18 visits	Y	Y		Y	Y		
Prescribed total daily basal insulin (insulin glargine) (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, 18, and 26 visits	Y	Y		Y	Y		

	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Prescribed total daily basal insulin (insulin glargine) (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, 18, and 26 visits	Y	Y		Y	Y		
Prescribed total daily bolus insulin (insulin lispro) (total units and total units/kg body weight) at the Baseline/Randomization and Week 4, 10, 18, and 26 visits	Y	Y		Y	Y		
Total number of weekly insulin injections (7 days) to achieve glycemic control at Baseline/Randomization and Week 4, 10, 18, and 26	Y	Y		Y	Y		
Composite endpoints (after 26 weeks of treatment): Percentage of subjects achieving HbA_{1c} <7.0% without weight gain	Y			Y			
Composite endpoints (after 26 weeks of treatment): Percentage of subjects achieving HbA_{1c} <7.0% without severe or documented symptomatic hypoglycemia	Y			Y			
Composite endpoints (after 26 weeks of treatment): Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without severe or documented hypoglycemia	Y			Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

8.1.2. Key Secondary Efficacy Endpoints

8.1.2.1. Proportion of Subjects Who Do Not Meet Prespecified Criteria for Severe, Persistent Hyperglycemia through Week 26

For this key secondary endpoint, subjects who do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26 will be defined operationally as those subjects treated with once-weekly albiglutide that are able to replace prandial insulin without lispro re-introduction through Week 26. Note: For lispro re-introduction through Week 26 the time window is defined up to Week 25.

Proportion of subjects that are able to discontinue insulin lispro at Week 4 and do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26 will be summarized descriptively for all the Albiglutide + Insulin Glargine arm subjects and for

subgroups of baseline HbA_{1c} category (<8.0%, ≥8.0%), region, (<65 years versus ≥65 years), current use of metformin (Yes, No) in the FA population. The 95% confidence interval of the proportions of subjects will be provided.

The insulin lispro that was re-introduced to albiglutide subjects will be characterized. Summary statistics for the number of injections, total dose, and time-to-re-introduction will be presented.

Additional exploratory analyses to identify potential risk factors for lispro re-introduction will be investigated. Potential risk factors include: baseline HbA1c, baseline HbA1c category, age, age category, metformin-use, duration of diabetes, weight, BMI, BMI category, time in insulin (at baseline), baseline HbA1c, and total insulin dose at baseline. Time in insulin (at baseline) is defined as the earliest start date of prior insulin medications taken minus the date of first date of randomized study medication, plus 1.

8.1.2.2. Percentages of Subjects with Severe or Documented Symptomatic Hypoglycemia through Week 26

The percentage of subjects with severe or documented symptomatic hypoglycemia will be summarized descriptively by treatment and analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by baseline HbA_{1c} category, region, age category (<65 years versus ≥65 years), current use of metformin (Yes, No) in the FA population.

As supportive analysis, logistic regression models adjusting for baseline HbA_{1c} category, region, age category and current use of metformin will be used to quantify the treatment effects. Odds ratio for treatment and the associated confidence interval will be used to estimate the treatment difference.

8.1.2.3. Change from Baseline in Body Weight at Week 26 and over Time

Change from Baseline in body weight will be analyzed and summarized analogous to the primary efficacy endpoint using a slightly different MMRM model which includes change from Baseline in body weight as dependent variable; treatment, region, baseline HbA_{1c} category, age category, current metformin use, visit week, treatment-by-week interaction, and baseline weight-by-week interaction as fixed effects; baseline weight as a continuous covariate; and subject as a random effect (Model 2). Treatment difference at Week 26 will be tested; p-value and 2-sided 95% confidence interval will be presented. The percentage change from baseline in body weight will be analysed using a similar MMRM model:

Change from Baseline in Body Weight = Baseline Body Weight + Treatment + Baseline HbA_{1c} Category + Region + Age Category + Current Use of Metformin + Visit Week + Treatment-by-Visit Interaction + Baseline Body Weight-by-Visit Week Interaction (Model 2).

The percentage change from Baseline in body weight will be analyzed similarly using Model 2 above, with percent change from baseline in body weight as the dependent variable.

The observed body weight values and change and percent change from baseline body weight will be summarized descriptively and presented graphically. The least squares means (and standard errors) of change from baseline body weight will be plotted by treatment group.

The analyses will be performed on FA population and all data will be listed.

8.1.2.4. Prescribed Total Daily Insulin Doses and Total Number of Weekly Insulin Injections

Prescribed total daily insulin doses at Baseline, Week 4, 5, 10, 18 and 26 will be assessed from several aspects:

- Total daily insulin dose (IU)
- Body weight adjusted total daily insulin dose (IU/kg)
- Total daily basal insulin (insulin glargine) dose (IU)
- Body weight adjusted total daily basal insulin (insulin glargine) dose
- Total daily bolus insulin (insulin lispro) dose (IU)
- Body weight adjusted total daily bolus insulin (insulin lispro) dose

The absolute value in each of the above variables by visit will be analyzed using an MMRM model similar to Model 2 where the specific insulin dose replaces weight (Section 8.1.2.3). The prescribed total daily insulin doses will be summarized descriptively and presented graphically by treatment group. The least squares means (and standard errors) of the prescribed total daily insulin doses will be plotted by treatment group.

In addition, total number of weekly insulin injections (7 days) to achieve glycemic control at Baseline, Week 4, 5, 10, 18 and 26 will also be assessed and summarized using descriptive statistics; the value for this analysis is derived based on the number of prescribed insulin injections as follows:

- Albiglutide: 1 injection per week
- Insulin Glargine: 1 injection per day (7 injections per week)
- Insulin Lispro: 3 injections per day (21 injections per week)

For subjects who was randomized to the albiglutide arm and required re-introduction of insulin lispro, the number of injections for insulin lispro should be based on data collected in the Surveillance eCRF page. These subjects could have once-daily, twice-daily or three times daily insulin lispro injections.

Definitions for insulin dose and number of injections at Week 26 for albiglutide arm:

- Both glargine and lispro dose at Week 26 will be defined operationally as the prescribed dose at Week 25.
- For lispro number of injections at Week 26 will be defined operationally as the prescribed number of injections at Week 25. For glargine number of injections at Week 26 will be considered 1 per day.

8.1.3. Supportive Secondary Efficacy Endpoints

8.1.3.1. HbA_{1c} Change from Baseline over Time

HbA_{1c} change from Baseline by visit will be analyzed analogous to the primary efficacy endpoint using the same MMRM model (Model 1) in the FA population. The observed HbA_{1c} and change from Baseline HbA_{1c} will be summarized descriptively and presented graphically. The least squares means (and standard errors) of change from Baseline HbA_{1c} will be plotted by treatment group.

8.1.3.2. FPG Change from Baseline at Week 26 and over Time

FPG change from Baseline by visit will be analyzed and summarized similarly to weight change from Baseline using Model 2 with FPG replacing weight in the model (Section 8.1.2.3). The analyses will be performed on FA population and all data will be listed.

Due to administrative error in the Time and Events table in the protocol, fasting plasma glucose (FPG) was not collected at Week 26 and will be imputed with fasting serum glucose (FSG) value. Correlation analyses of FPG and FSG values using data from this trial at earlier visit as data allows will be performed to provide an assessment of the validity of this imputation.

8.1.3.3. Proportion of Subjects Achieving HbA_{1c} <7% at Week 26 and over Time

The proportion of subjects achieving HbA_{1c} target values of <7.0% at Week 26 and over time will be summarized by treatment and visit for the FA population. The treatment comparison will be carried out using the CMH test and logistic regression model described in Section 8.1.2.2. The proportion of subjects who responded over time will also be plotted using a bar chart.

If a subject has a missing HbA_{1c} value at week 26 and the reason why value is missing is not related to efficacy or safety (e.g., procedural) and could be assumed that value is missing at random, then the value will be left as missing for calculations; if the reason why value is missing is lack of efficacy or due to safety, then this missing value will be imputed as ‘not meeting target’ and included in the denominator in the calculation of the proportion of subjects achieving target HbA_{1c} <7%.

The results with the observed data and with imputed data will be both presented as part of sensitivity analysis.

8.1.3.4. Proportion of Subjects Achieving HbA_{1c} <6.5% at Week 26 and over Time

Proportion of subjects achieving HbA_{1c} target values of <6.5% at Week 26 and over time will be analyzed and summarized in a similar manner as specified in Section 8.1.3.3.

8.1.3.5. Incidence and Time to Meeting Prespecified Criteria for Severe, Persistent Hyperglycemia through Week 26

In this treat-to-target study design, subjects may be withdrawn if they have severe and persistent hyperglycemia. Meeting prespecified criteria for severe, persistent hyperglycemia at week 26 will be defined operationally as being withdrawn due to lack of efficacy as recorded on the Treatment Discontinuation and Study Conclusion eCRF pages. Proportion of subjects who meet prespecified criteria for severe, persistent hyperglycemia at Week 26 will be summarized and analyzed in a same manner as described in Section 8.1.2.2.

The time to meeting prespecified criteria for severe, persistent hyperglycemia through Week 26 will be calculated as the number of days between the date of first dose of randomized study medication and the date of meeting prespecified criteria, persistent hyperglycemia, plus 1. Subjects who do not meet the criteria will be censored at the date of the Week 26 visit or the date of the early termination visit if the subject terminated the study early. Kaplan-Meier estimates of the median time to meeting the criteria and 95% confidence interval for each treatment group will be presented. The treatment difference will be assessed using a log-rank test. The proportion of subjects meeting the criteria up to Week 26 (Day 182) based on Kaplan-Meier estimates will be displayed in the summary table. Kaplan-Meier curves of the times to meeting the criteria for each treatment group will be presented.

The analysis will be performed on FA population and all data will be listed.

8.1.3.6. Composite Endpoints

The following composite endpoints (after 26 weeks of treatment) will be analyzed as secondary efficacy endpoints:

- Percentage of subjects achieving HbA_{1c} <7.0% without weight gain
- Percentage of subjects achieving HbA_{1c} <7.0% without severe or documented symptomatic hypoglycemia
- Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without severe or documented symptomatic hypoglycemia

No weight gain is defined as ≤1 kg increase from baseline in body weight. These composite endpoints will be analyzed and summarized in a similar manner as specified in Section 8.1.2.2.

8.2. Exploratory Efficacy Analyses

8.2.1. Overview of Planned Exploratory Efficacy Analyses

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

Table 5 provides an overview of the planned exploratory efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 5 Overview of Planned Exploratory Efficacy Analyses

	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Exploratory Endpoints							
Patient-reported outcomes to diabetes medication at Baseline/Randomization, Week 10, and Week 26: Treatment-related impact measure for diabetes (TRIM-Diabetes) questionnaire	Y			Y			Y
Patient-reported outcomes to diabetes medication at Baseline/Randomization, Week 10, and Week 26: Hypoglycemia fear survey-II (HFS-II) worry subscale	Y			Y			Y
HbA_{1c} change from Baseline at Week 26 by baseline FPG tertiles	Y			Y			Y
FPG change from Baseline at Week 26 by baseline FPG tertiles	Y			Y			Y
24-hour glucose profile: 8-point self-monitored blood glucose (SMBG) profile at Baseline/Randomization, Week 10, and Week 26 (before and 120 minutes after the 3 main meals, at bedtime, and at 2 AM)	Y			Y	Y		Y
Mean daily blood glucose based on the 8-point SMBG profile at Baseline/Randomization, Week 10, and Week 26	Y			Y			Y
Number (and percentage) of subjects with <=1 kg weight gain at Week 26	Y			Y			Y
Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L) regardless of symptoms at Week 26	Y			Y			Y
Proportion of subjects treated with once-weekly albiglutide that are able to totally replace or decrease prandial insulin without worsening HbA_{1c} control (worsening defined as >0.3% increase in HbA_{1c} compared with baseline HbA_{1c}) at Week 26	Y			Y			Y
Genetic sampling							
Novel biomarker analysis	TBD	TBD	TBD	TBD	TBD	TBD	TBD

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 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.
TBD = to be determined after review of efficacy and safety data at the end of the study or other emerging information that may become available during the study

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

8.2.2. TRIM-Diabetes Questionnaire

The TRIM-Diabetes questionnaire is a 28-item treatment satisfaction measure with 5 domains assessing treatment burden, daily life, diabetes management, compliance, and psychological health. Measures can be scored independently for each domain or as a total score. Higher scores indicate a better health state.

The TRIM-Diabetes will be administered in this study at baseline, Week 10, and Week 26 to assess treatment satisfaction within each treatment group of the study.

There are three steps for the calculation of TRIM- Diabetes scores. The first step is to reverse the coded value for questions in daily life, compliance, and psychological health domains, so that a higher score indicates better health for all domains. In the second step, raw scale scores are computed by summing across items in the same domain (raw domain scores). A total raw score can also be calculated. In last step, raw scale scores are transformed to a 0-100 scale (transformed scale scores) using the following: Domain= [(raw score - lowest possible raw score) / possible raw score range] x 100.

Change from baseline in TRIM-Diabetes total score and individual domain scores will be summarized descriptively by visit and treatment group, and analyzed using a similar MMRM model as Model 2 where TRIM-Diabetes scores replace weight.

Every effort will be made to minimize the amount of missing data and therefore maximize the quality of the data collected. If a patient answers at least half of the items in a multi-item domain (or half plus one in the case of domains with an odd number of items) then a domain score should be calculated. The average score (across completed items in the same domain) for that patient will be used to estimate any missing item in that domain. For example, if a patient leaves a blank item in the 5-item Diabetes Management domain, substitute the patient's average score (across the four answered Diabetes Management items) for the score for that item.

If more than one answer is ticked off by the patient (adjacent answers or not) the item should be coded as missing.

8.2.3. HFS-II Worry Subscale

The HFS-II questionnaire is a 33-item questionnaire with 2 subscales that measure: 1) behavior to avoid hypoglycemia and its negative consequences and 2) worries about hypoglycemia and its negative consequences. This study will include the worry subscale only (18 items, score range 0 to 72). Responses use a 5-point Likert scale ranging from Never to Always. The HFS-II has a 6-month recall period.

The HFS-II will be administered in this study at baseline, Week 10, and Week 26 to assess within each treatment group worries about hypoglycemia.

The continuous endpoint of HFS-II worry subscale score change from Baseline by visit will be analyzed using an MMRM model similar to Model 2 where HFS-II worry subscale score replaces weight.

If a subject missed one or more items, or ticked multiple items, the data will be handled in the same as for TRIM-Diabetes questionnaire items.

8.2.4. HbA_{1c} Change from Baseline at Week 26 by Baseline FPG Tertiles

The minimum, 33% percentile, 66% percentile and the maximum values of baseline FPG concentration will be obtained from the valid FPG values at baseline. The subjects will be stratified into 3 groups with their baseline FPG concentration <33% percentile (1st FPG Tertile), ≤33% to <67% percentile (2nd FPG Tertile), and the rest (3rd FPG Tertile). HbA_{1c} values will be summarized descriptively by baseline FPG tertiles, by visit and treatment. The MMRM model for the subgroup analysis on the primary efficacy endpoint (Section 7.1.1.3) will be used in the FA population for this analysis.

8.2.5. FPG Change from Baseline at Week 26 by Baseline FPG Tertiles

This endpoint will be summarized descriptively and analyzed using a similar model as used for the analysis in Section 8.2.4, with FPG change from baseline as the response variable and adding baseline FPG tertile as covariate (Refer to Appendix 11 for model specification and SAS code).

8.2.6. 8-Point SMBG Profile and Mean Daily Blood Glucose

An 8-point blood glucose profile will be performed by the subject 3 times in the week prior to Baseline, Week 10 and Week 26. Subjects will be instructed to measure and record glucose values from their glucose meter at the following times:

- 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
- At 2 AM

Glucose concentrations at each of the 8 time points will be averaged over three days with the largest count of 8-point SMBG data points within the visit window to derive the mean glucose concentrations at each time point. If there are ties for these counts within the visit window, select the one closest to the actual visit day. If subject only had 1 or 2 days of 8-point SMBG within the visit window, use 1 day 8-point SMBG or average of 2 days of 8-point SMBG data. The daily average of glucose concentrations will be calculated as the average over the glucose concentrations at the 8 time points. The daily average data will be calculated only if at least one pair of preprandial and postprandial glucose values is available. Only complete pairs of preprandial and postprandial glucose values will be used for the calculation.

Visit window will be defined for the purpose of SMBG calculation. It will be defined by study day according to following table.

Table - Visit Window for SMBG Calculation

Visit	Target Study Day	Range of Study Day
Baseline	1	Study day <= 1
Week 10	71	43 <= study day <= 99
Week 26	183	155 <= study day <= 211

The absolute glucose concentrations and change from Baseline at each time point will be summarized descriptively by treatment and visit for the FA population. The daily average glucose concentration and change from Baseline will be summarized similarly. The absolute glucose concentrations will also be plotted by visit, time points and treatment.

Daily average glucose concentrations will be analyzed similarly to weight, with a MMRM model (Model 2) with daily average glucose replacing weight in the model (Section 8.1.2.3). The analyses will be performed on FA population and all data will be listed.

8.2.7. Number and Percentage of Subjects with ≤1 kg Weight Gain at Week 26

Number and percent of subjects with <=1 kg weight gain at Week 26 will be analyzed in the same manner as specified in Section 8.1.2.2.

8.2.8. Percentage of Subjects Achieving HbA_{1c} <7.0% without Weight Gain and without Hypoglycemia with Blood Glucose <3.1 mmol/L (<56 mg/dL) regardless of Symptoms at Week 26

This composite endpoint will be analyzed in the same manner as specified in Section 8.1.2.2.

8.2.9. Proportion of Subjects Treated with Once-Weekly Albiglutide That Are Able to Totally Decrease Prandial Insulin without Worsening HbA_{1c} Control at Week 26

Worsening HbA_{1c} is defined as >0.3% increase in HbA_{1c} compared to baseline at Week 26. This exploratory endpoint will be analyzed in the same manner as specified in Section 8.1.2.1.

8.3. Safety Analyses

8.3.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population.

Table 6 provides an overview of the planned analyses with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 6 Overview of Planned Safety Analyses

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
All AEs	Y			Y				
Treatment-Emergent AEs	Y			Y				
Relationship of AEs to Study Drug	Y			Y				
AEs by Maximum Intensity	Y			Y				
Most Common AEs	Y			Y				
Serious AEs	Y			Y				
AEs and SAEs Leading to Treatment Discontinuation	Y			Y				
Fatal AEs and non-fatal SAEs	Y			Y				
AEs of special interest	Y			Y				
Severe, documented symptomatic, and asymptomatic hypoglycemic events in 3-month	Y							
Incidence of hypoglycemic events (in total and by each category as defined by the American Diabetes Association criteria)	Y							
Incidence of daytime hypoglycemia (in total and by category), and nocturnal hypoglycemia (in total and by category)	Y							
Incidence of hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L), regardless of symptoms	Y							
Clinical Laboratory	Y	Y		Y	Y	Y		Y
Vital Signs	Y	Y		Y	Y	Y		Y
Electrocardiogram (ECG)	Y	Y		Y	Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

8.3.2. Adverse Events

All AEs will be coded using MedDRA which will be updated whenever available throughout the life of the study. Adverse events will be categorized by their occurrence in regard to therapeutic phase (pre-therapy, on-therapy, or post-therapy) as defined in Appendix 4. Adverse events will be summarized in various subsets by treatment group. An overview summary of the number and percentage of subjects with any AE, the total number of AEs recorded, and the overall AE density and incidence rate for on-therapy AEs will be provided by treatment group. The overview will also summarize SAEs, treatment-related AEs, AEs by maximum intensity, and AEs by therapy phase.

Summaries of the number and percentage of subjects with any treatment-emergent AEs (TEAEs), related AEs, AEs leading to treatment discontinuation or withdrawal from study, SAES, fatal AEs etc, will be provided. Adverse events will also be summarized by maximum intensity (mild, moderate, and severe).

Except summaries for serious AEs, AEs leading to withdrawal from treatment or pre-therapy AEs, all other AE summaries do not include hypoglycemic events, unless otherwise specified.

All AEs will be listed in a subject data listing.

8.3.2.1. General Adverse Events Summaries

Summaries of the number and percentage of subjects with AEs and the total number of AEs will be provided by treatment group overall and at the SOC and PT level for the following time periods:

1) On-therapy and post-therapy combined period
2) Pre-therapy (includes hypoglycemia events)
3) On-therapy
4) Post-therapy

In addition, on-therapy Adverse events will be presented by time intervals of onset (<=12 weeks, >12 - <=26 weeks) and by treatment group; the on-therapy non-serious AEs will be summarized by treatment group.

An additional on-therapy AE summary will also be provided following government clinical register format; these summaries will include the AEs of hypoglycemia event.

A by-subject listing of all AEs will also be presented.

8.3.2.2. Treatment Emergent Adverse Events

TEAEs are defined as any AEs, regardless of relationship to the, randomized study drug (i.e., albiglutide or other study treatments), that occur after the first dose of the

randomized study medication, which is equivalent to on-therapy and post-therapy AEs combined. Summaries of the number and percentage of subjects with TEAEs will be provided by treatment group overall at the SOC and PT level. TEAES will also be further defined as on-therapy or post-therapy AEs for summary purposes.

A by-subject listing of all TEAEs will also be presented.

8.3.2.3. Treatment-Related Adverse Events

Treatment-related AEs will be defined as any AEs that are considered by the investigator to have a reasonable possibility to be related to the study treatment. If a relationship to the study treatment is missing or unknown after the start of treatment it will be assumed, for the purpose of analyses, to be treatment-related.

A summary of the number and percentage of subjects with treatment-related AEs will be displayed. The treatment-related AE data will be categorized and presented in a manner similar to that described above for the general AE summaries for both the on-therapy and post-therapy therapeutic phases.

8.3.2.4. Adverse Events by Maximum Intensity

A summary of the number and percentage of subjects with on-therapy and post-therapy adverse events by intensity (mild, moderate, and severe) will be produced. The data will be sorted and categorized using the method and format described previously.

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 summarization.

8.3.2.5. Most Common Adverse Events

A summary of most common on-therapy adverse events (>2% total incidence in any treatment arm) by treatment will be produced.

In addition, on-therapy non-serious AEs with proportion of subjects experiencing the AE >=5% among any of the active arms will be summarized by treatment group following government clinical register format; this summary will include AEs of hypoglycemia event.

8.3.3. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarized in a manner similar to that described above for the general AE summaries by treatment group for pre-therapy, on-therapy, and post-therapy therapeutic phases. Treatment-related SAEs will also be summarized separately by treatment group for both the on-therapy and post-therapy therapeutic phases.

SAE, fatal SAE and serious non-fatal AEs will also be summarized following government clinical register format; these summaries will include SAEs of hypoglycemia event.

Summaries and by subject listings of fatal AEs and serious non-fatal AEs will be presented.

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

A summary of the number and percentage of subjects with adverse events leading to permanent discontinuation of the randomized study drug (that is, withdrawal of active treatment) will be presented by treatment group for the on-therapy phase.

A by-subject listing of all adverse events leading to permanent discontinuation of study drug/withdrawal from the study will be produced.

8.3.5. Adverse Events of Special Interest

For selected AEs of special interest such as hypoglycemia, the exposure-adjusted event rate, i.e., AE density, will be calculated as the number of events in a given period divided by the total person time on treatment of subjects at risk within the same period; the exposure-adjusted incidence rate will also be calculated as the number of subjects in a given period divided by the total person time on treatment of subjects at risk within the same period. The exposure-adjusted event rate and incidence rate will be expressed as an annualized rate (expected number of events or subjects per 100 person-years).

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

8.3.5.1. Hypoglycemic Events

Hypoglycemic events merit special attention in the development and study of drugs for the treatment of T2DM since they are often related to the efficacy of a compound. In order to accomplish this, hypoglycemic event data including supplemental hypoglycemic event information not collected on AE eCRF page are reported on a separate hypoglycemic event eCRF page. However, any hypoglycemic event that meets the criteria for a serious AE will also be included in the serious AE summaries.

Analysis of on-therapy hypoglycemic events will include all AEs coded to the preferred term of ‘Hypoglycemia’. For on-therapy hypoglycemic events the number and percentage of subjects with events, the number of events, the incidence rate (per 100 person-years) and AE density (per 100 person-years) by the severity of the event defined by American Diabetes Association [ADA], SAE status, relationship to the investigational product, and withdrawal status will be summarized by treatment group. The events will also be summarized according to intervention provided, action taken with regard to background and anti-hyperglycemic medications and onset week and glucose levels. All hypoglycemic events will be classified as severe, documented symptomatic,

asymptomatic, probable symptomatic, or pseudohypoglycemia per the American Diabetes Association criteria) criteria.

The number of events of hypoglycemia with confirmed home blood glucose monitoring < 3.9 mmol/L and/or requiring third party intervention (i.e., severe, documented symptomatic and asymptomatic hypoglycemic events) in 3 monthly intervals (i.e., from Baseline to Week 12, >Week 12 to Week 26) will be summarized by treatment group. The exposure-adjusted event rate will be compared between treatment groups using a Poisson regression model with offset for the person-year, which will include HbA_{1c} stratum, age (<65 years versus ≥65 years), current use of metformin (metformin use versus no metformin use), and region as covariates.

Incidence (in total and by each category) of hypoglycemia, daytime hypoglycemia, and nocturnal hypoglycemia will be summarized by treatment group. Daytime hypoglycemia is defined as hypoglycemic events with an onset between 06:00 hours and 00.00 hours (inclusive). Nocturnal hypoglycemia is defined as hypoglycemic events with an onset between 00:01 hour and 05:59 hours (inclusive). The incidence of hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L), regardless of symptoms, will also be summarized by treatment group.

On-therapy hypoglycemic events over time will be summarized by onset week and plotted for each treatment group.

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

8.3.5.2. Cardiovascular Events

A summary of the number and percentage of subjects with cardiovascular events will be reported by treatment group and therapeutic phase.

A by-subject listing of all the data elements collected on the eCRF page will be presented for subjects who experience cardiovascular events.

8.3.5.3. Pancreatitis and Pancreatic Cancer

The number and percent of subjects with pancreatitis and pancreatic cancer will be reported by treatment group. A by-subject listing of all the data elements collected on pancreatitis event page of the eCRF will be presented for subjects who experienced pancreatitis and pancreatic cancer. This listing of the pancreatitis events will also include the adjudication results as determined by the independent pancreatitis adjudication committee.

8.3.5.4. Thyroid Adverse Events

The number and percent of subjects with thyroid AEs will be reported by treatment group. Additionally thyroid adverse events identified by a customized MedDRA query will be presented by treatment group.

A by-subject listing of all the data elements captured in the thyroid tumor eCRF page will be produced.

8.3.5.5. 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 and therapeutic phase (pre-, on-, or post-therapy). Also, summaries of on-therapy GI events that lead to withdrawal of active treatment, treatment-related and serious GI events (including those that do not necessarily lead to withdrawal of active treatment) will be presented separately by treatment group.

For each subject, the time to first occurrence of a GI event is calculated as the number of days between the randomization date and the date of onset of the first on-therapy GI event plus 1. Subjects who do not experience any GI events will be censored at the last dose date plus 25 days in the albiglutide arm or within the last dose date in the lispro arm. The median time to first occurrence of a GI event as well as the Kaplan-Meier probability of first occurrence of a GI event at various time points will be presented for each treatment group. Kaplan-Meier curves for the time to first occurrence of a GI event for each treatment group will also be presented.

The prevalence of GI events will be reported and plotted by treatment group.

The number and percentage of subjects reporting nausea at each study week will be presented by treatment group. Each week will include those subjects with onset of nausea during that particular week and also those subjects with nausea that started during a previous week but has not resolved. The prevalence of nausea will also be plotted over time. Similar summaries and plots will be presented for subjects reporting events of diarrhea and also separately for subjects reporting events of vomiting. In addition, a combined summary and accompanying plot of the number and percentage of subjects reporting events of nausea and/or vomiting will be presented.

8.3.5.6. Systemic Allergic Reactions

Systemic allergic reactions are reported by the investigators on the eCRF. The number and percentage of subjects with suspected systemic allergic reactions will be presented by treatment group. In addition, the time to first occurrence of a systemic allergic reaction will be analyzed and presented in a manner identical to that described above for first occurrence of a GI event.

A summary of systemic allergic reactions based on customized MedDRA query (CMQ) list identified by GSK will also be presented. Analyses will be repeated for this data.

8.3.5.7. Injection Site Reactions

Injection site reactions are reported by the investigators on the eCRF. The number and percentage of subjects with injection site reactions will be presented. In addition, the time to first occurrence of an injection site reaction will be analyzed and presented in a manner identical to that described above for first occurrence of a GI event.

The number and percentage of subjects reporting injection site reactions at each study week will be presented by treatment group. Each week will include those subjects with

the onset of an injection site reaction during that particular week as well as those subjects with injection site reactions from previous weeks that have not resolved. The incidence of injection site reactions will be plotted over time. Various characteristics of injection site reactions at the event level and subject level will be summarized.

A by-subject listing of injection site reactions will also be produced.

8.3.5.8. Liver Events

The number and percentage of subjects with liver events that have been identified by investigators on the liver events eCRF page will be presented by treatment group. Additionally, liver events identified by a customized MedDRA query will also be presented by treatment group. By-subject listings of all the data elements collected on the eCRF page will be presented for subjects who experience adverse liver events, as identified by the investigators.

8.3.5.9. Atrial Fibrillation/Flutter

The number and percentage of subjects with Atrial Fibrillation/Flutter events will be presented by treatment group for Atrial Fibrillation and Atrial Flutter. By-subject listings of all the data elements collected on the Atrial Fibrillation and Atrial Flutter event eCRF page will be presented for subjects who experience atrial fibrillation/flutter events, as reported by the investigators.

8.3.5.10. Pneumonia

The number and percentage of subjects with Pneumonia events will be presented by treatment group for Pneumonia event reported by the investigator on the eCRF. Summary of Pneumonia events identified by a selected list of preferred terms will also be provided. By-subject listings of all the data elements collected on the Pneumonia event eCRF page will be presented for subjects who experience pneumonia events, as reported by the investigators.

8.3.5.11. Diabetic Retinopathy

The number and percentage of subjects with diabetic retinopathy events will be presented by treatment group. A by-subject listing of all the data elements collected on the diabetic retinopathy eCRF page will be presented for subjects who experience diabetic retinopathy, as reported by the investigators.

8.3.5.12. Appendicitis

The preferred terms containing the word “appendicitis” will be identified as Appendicitis events. The number and percentage of subjects with appendicitis will be presented by treatment group and a by-subject listing will be presented.

8.3.5.13. Malignant Neoplasm

Malignant neoplasm will be captured in the AE eCRF pages. The number and percentages of subjects with malignant neoplasm identified by a customized MedDRA query will be presented by treatment group and a by-subject listing will be presented.

8.3.6. Pregnancies

A listing of subject pregnancies will be provided.

8.3.7. Clinical Laboratory Evaluations

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 summarization.

8.3.7.1. Chemistry, Hematology and Urinalysis

Laboratory parameters include the following tests: hematology, chemistry and urinalysis. Established or generally acknowledged methods, normal ranges, and quality control procedures will be supplied by Quest Diagnostics Clinical Laboratory for the study records.

Hematology parameters used in summaries include complete blood count with red blood cell indices, white blood cell count differential, and platelet count. Chemistry parameters (including lipids) used in summaries include glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), ALT, aspartate aminotransferase (AST), gamma-glutamyltransferase, uric acid, magnesium, phosphorus, eGFR, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides. Urinalysis parameters used in summaries include specific gravity, pH, glucose, ketones, microalbumin, creatinine, blood, leukocyte esterase, and nitrites.

All laboratory parameters will be summarized, for each treatment group, at every scheduled assessment time point using descriptive statistics and presented graphically. In addition, for hematology and chemistry laboratory parameters, change from Baseline in these quantitative tests will be summarized by treatment group and at every scheduled assessment postbaseline time point. Shift tables providing the number and percentage of subjects with indicated shifts (normal, abnormal not of clinical concern, abnormal of clinical concern) in their results from baseline to each scheduled postbaseline assessment will also be presented for all hematology and chemistry parameters.

Additionally, the number of subjects with laboratory values of potential clinical concern will be summarized by treatment group and scheduled assessment time point for hematology and chemistry. The criteria for laboratory values of potential clinical concern are detailed in Appendix 7: Values of Potential Clinical Importance.

A summary of laboratory values of potential clinical concern will be provided for liver function tests, including ALT, AST, and total bilirubin. The criteria for liver function

tests of potential clinical concern are detailed in Appendix 7: Values of Potential Clinical Importance.

All summaries will be done for the safety population and all laboratory data will be listed including hepatitis B, hepatitis C, fasting C-peptide, TSH, and urine pregnancy test results.

8.3.7.2. Albumin/Creatinine Ratio

The pattern of urine albumin to creatinine ratio (UACR) over time and change from Baseline over time will be evaluated descriptively using summary statistics and graphically at each scheduled visit. Change from Baseline of each of the ratios will be calculated as postbaseline value divided by baseline value. A value less than 1 represents a decrease from baseline and a value greater than one represents an increase from baseline. Shift tables providing the number and percentage of subjects with indicated shifts (normal, abnormal not of clinical concern, abnormal of clinical concern) in their results from baseline to each scheduled postbaseline assessment will also be presented.

The analysis will be performed on safety population and all data will be listed.

8.3.8. Other Safety Measures

8.3.8.1. Vital Signs

The vital sign summary and analysis will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm).

Each vital sign parameter at every scheduled assessment time point will be summarized using descriptive statistics and presented graphically. Change from Baseline will also be summarized using descriptive statistics and presented graphically. Additionally, the number of subjects with vital signs of potential clinical concern will also be summarized. Shift tables providing the number and percentage of subjects with indicated shifts (normal, low value of clinical concern, high value of clinical concern) in their results from baseline to each scheduled postbaseline assessment will also be presented. The criteria for vital signs of potential clinical concern are detailed in Appendix 7: Values of Potential Clinical Importance.

All summaries will be done for the safety population and all vital sign data will be listed.

8.3.8.2. Electrocardiograms

ECG parameters collected at each scheduled assessment time point include heart rate, QRS interval, QT interval, QT interval – Bazett correction (QTcB), QT interval – Fridericia correction (QTcF), RR interval and PR interval.

Each ECG parameter at each scheduled assessment time point will be summarized by treatment group using descriptive statistics and presented graphically. Change from Baseline will also be summarized using descriptive statistics. A summary of the number and percentage of subjects in overall ECG interpretation and abnormal findings will be displayed by treatment group. The number of subjects with ECG values of potential

clinical concern will also be summarized. Shift tables providing the number and percentage of subjects with indicated shifts (normal, low value of clinical concern, high value of clinical concern) in their results from baseline to each scheduled postbaseline assessment will also be presented. The criteria for ECG values of potential clinical concern are detailed in Appendix 7: Values of Potential Clinical Importance.

Additionally, categorical summaries for QTcB and QTcF values (>450, >480, and >500 msec) and QTcB and QTcF change from Baseline values (>30, and >60 msec) will be presented by visit and treatment group.

All summaries will be done for the safety population and all ECG data will be listed.

8.3.8.3. Physical Exams

In this study, findings from physical exams will be recorded in the AE eCRF page or medical history CRF page by the investigator as deemed appropriate. No separate summary of physical exams will be provided.

8.4. Biomarker data analyses

After completion of the clinical trial, if biomarker investigations are performed on samples collected during the study, the results will be reported separately from the main clinical study report.

8.5. Pharmacogenetic data analyses

Additional blood samples drawn for pharmacogenetic (PGx) analysis will be stored and may be analyzed in the future for exploratory study of variability in drug response because of hereditary factors in different populations. Whenever applicable, the details of these analyses will be described in a separate document. See the protocol for details about the Pharmacogenetics Analysis Plan.

8.6. Immunogenicity

In the case of severe systemic allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions that cannot reasonably be attributed to another cause, five 1-mL serum samples should be obtained for immunogenicity testing (within 24 hours of the event if possible) and sent to the central laboratory (see details in the SPM) for immediate distribution to contracted testing facility for specific immunological testing (albiglutide-specific immunoglobulin E and other tests, as appropriate). A follow-up serum sample will be taken 8 weeks after final dose of study treatment in these subjects. If data is available, a listing will be created to display immunogenicity testing.

8.7. Clinical Pharmacology Data Analysis

Not applicable.

9. OTHER STATISTICAL ANALYSES

Not Applicable.

10. REFERENCES

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11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Time and Events
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Treatment Periods
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: Multicentre Studies and Definition of Geographic Region for Statistical Analyses
Section 11.9	Appendix 9: Examination of Covariates and Subgroups
Section 11.10	Appendix 10: Multiple Comparisons and Multiplicity
Section 11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 11.12	Appendix 12: Sample Size Considerations
Section 11.13	Appendix 13: Abbreviations & Trade Marks
Section 11.14	Appendix 14: List of Data Displays

11.1. Appendix 1: Significant Protocol Deviation Plan and Definitions for Per-Protocol Population

11.1.1. Definitions for Per-Protocol Population

The per-protocol population is a subset of the full analysis population including all subjects who were randomized, have completed Week 26 treatment, and overall compliance greater than or equal to 80%.

11.1.2. Significant Protocol Deviation Plan and Definitions for Per-Protocol Population

The Significant Protocol Deviation Plan Version 1, dated 18 Sep 2015 will be used to identify the significant protocol deviations. It is intended to categorize significant protocol deviations that are anticipated to occur in a study and to document study-specific requirements for cross-functional team review of these significant protocol deviations and other deviations that may occur in the study.

Part A of the Significant Protocol Deviation Plan is a list of the frequency that all deviations (protocol and GCP) will undergo review by a cross-functional team. (Review should assess trending and appropriate categorization (both deviation type and significance)).

Part B is a list of each significant protocol deviation in the appropriate category and indicates the criterion that makes the deviation significant. Non-significant deviations should not be included.

This Significant PD Rules document should be updated when changes are identified (e.g., new deviation, re-classification of significance of a deviation). The revised document should describe changes in the Change History and appropriate version control should be applied.

The executed Protocol Deviation Plan will be maintained in the PPD electronic Trial Master File (eTMF). GSK and PPD team members will have access to the Plan, including any amendments.

11.2. Appendix 2: Time & Events

11.2.1. Scheduled Clinic Visits

Table 5 and Table 6 of the protocol (Note: the tables and sections referred there are also from the protocol, not from this RAP)

Table 5 Time and Events Table – Study Visits

Study Procedure		Screening	Standardization		Treatment (For scheduled telephone calls, see Table 6)						Early Withdrawal Visit[1]	Follow-up Visit
					Baseline/ Randomization							
	Visit	1	2	3	4	5	6	7	8	9		10
	Week[2]	-6 to -5	-4[3]	-1	0[3]	4	5[3]	10[3]	18[3]	26[3,4]		30
Obtain written informed consent		x										
Obtain subject demography		x										
Obtain medical history		x										
Obtain disease history		x										
Obtain therapy history		x										
Review of inclusion/exclusion criteria		x	x	x	x							
Review of randomization criteria					x							
Efficacy Assessments												
Dispense home glucose monitoring device and e-diary			x									
Collect e-diary from subject												x
Provide advice on diet, exercise, home glucose monitoring, and hypoglycemia[5]			x	x	x	x	x	x	x	x	x	x
Obtain 8-point SMBG profile[6]					x			x		x		
Review glucose monitoring with subject[5]				x	x	x	x	x	x	x	x	x
Administer diabetes questionnaires[7]					x			x		x	x	
Obtain daily insulin dose information[8]					x	x	x	x	x	x	x	
Safety Assessments												
Review concomitant medication		x	x	x	x	x	x	x	x	x	x	x
Perform physical examination[9]		x			x			x		x	x	
Check visual acuity and funduscopy[10]		x								x	x	
Obtain vital sign measurements[11]		x	x	x	x	x	x	x	x	x	x	x
Obtain body mass index information[11]		x										
Perform 12-lead ECG[12]		x			x					x	x	
Assess for adverse events			x	x	x	x	x	x	x	x	x	x
Assess for serious adverse events		x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycemic events[13]			x	x	x	x	x	x	x	x	x	x

Study Procedure		Screening	Standardization		Treatment (For scheduled telephone calls, see Table 6)						Early Withdrawal Visit[1]	Follow-up Visit
					Baseline/ Randomization							
	Visit	1	2	3	4	5	6	7	8	9		10
	Week[2]	-6 to -5	-4[3]	-1	0[3]	4	5[3]	10[3]	18[3]	26[3,4]		30
Laboratory Assessments												
Subject to fast overnight[14]		x		x	x	x	x	x	x	x	x	
Obtain hematology sample[15]		x			x			x		x	x	x
Obtain chemistry sample[16]		x		x[17]	x	x[18]	x[18]	x	x[18]	x	x	x
Obtain urinalysis sample[19]		x			x					x	x	
Obtain TSH sample[20]		x										
Obtain genetics sample[21]					x							
Obtain urine pregnancy test[22]		x			x			x		x	x	x
Obtain HBsAg and hepatitis C antibody[23] samples		x										
Obtain HbA_{1c} sample		x[24]		x[25]	x	x	x	x	x	x	x	
Obtain fasting C-peptide sample[26]		x										
Obtain stimulated C-peptide sample 90 minutes after administration of a mixed-meal[26]		x										
Obtain lipid panel[27]		x			x			x		x	x	
Obtain biomarker sample					x					x	x	
Investigational product												
Dispense investigational product or insulin glargine and insulin lispro[28]			x	x	x	x		x	x	x	x	
Assess investigational product and other study treatment compliance					x	x		x	x	x	x	x
Reduce or discontinue insulin lispro (albiglutide treatment group ONLY)[29]					x	x						
Albiglutide uptitration to 50 mg (albiglutide treatment group ONLY)						x						
Review the need for insulin glargine and/or insulin lispro adjustment[30]			x	x	x	x	x	x	x	x	x	
Register the subject's visit into the IVRS[31]		x	x	x	x[31]	x	x	x	x	x	x	

ECG = electrocardiogram; HbA_{1c} = glycosylated hemoglobin, HBsAg = hepatitis B surface antigen; IVRS = interactive voice response system; TSH = thyroid-stimulating hormone.

1. After completion of the early withdrawal assessments, subjects should return 4 weeks later for the Follow-up visit. In subjects who are withdrawn from the study due to an allergic or hypersensitivity reaction that is not reasonably attributed to another cause, a serum sample will be taken 8 weeks after stopping study medication for immunogenicity testing.
2. Study visits through Week 16, inclusive, will have a visit window of ±3 days; study visits occurring after Week 16 will have a visit window of ±7 days. Subjects will not be considered out of compliance if visit windows extend because of extraordinary events (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation will be at the discretion of the medical monitor.
3. Telephone calls to occur between study visits (if no study visit is scheduled, weekly from the start of the Standardization Period through Week 16, inclusive, and at Week 22, 25, and as required until the end of the Treatment Period [Table 6]) to advise subjects on insulin glargine and insulin lispro dose adjustments (see Section 5.1.1 and Section 5.1.3.2), adverse event monitoring, hypoglycemia monitoring, and concomitant medication usage.
4. The last dose of albiglutide is Week 25 for those subjects assigned to albiglutide + insulin glargine.
5. Standard diabetic dietary, exercise, and home blood glucose monitoring advice to be provided at Visit 2 (Week -4) and reinforced at each study site visit through the end-of-treatment visit. Subjects will monitor their glucose according to instructions. The investigator will review the glucose meter readings and adjust insulin glargine and insulin lispro doses in accordance with product labeling in the respective country and standard of care at the study center during the Standardization Period and per Table 3 and Table 4, respectively, during the Treatment Period. At each visit through the end-of-treatment visit (Visit 9; Week 26), subjects should be trained on the signs and symptoms of hypoglycemia, including nocturnal hypoglycemia, as well as the common causes of hypoglycemia. Subjects should also be educated on appropriate methods to help prevent hypoglycemia. It is also particularly important to advise subjects to contact the study site before any potential dietary change, as this may necessitate a change in insulin doses to avoid the development of hypoglycemia. Subjects should also be educated on how to treat hypoglycemia. For additional information, see Section 6.3.1.
6. An 8-point SMBG profile assessment (before and 2 hours after breakfast, lunch, and dinner; at bedtime; and at 2 AM): 3 times in the week prior to the Baseline/Randomization visit (Visit 4, Week 0), Visit 7 (Week 10), and Visit 9 (Week 26).
7. Treatment-related impact measure for diabetes (TRIM-Diabetes) and hypoglycemia fear survey-II (HFS-II) questionnaires to be administered prior to all other study assessments.
8. Daily insulin use to be recorded in the subject diary, at least 3 days preceding study visit/telephone contact at Week 1 through Week 16, inclusive, and at Week 18, 22, 25, and 26.
9. Perform complete physical examination at Screening and Week 26. Perform brief physical examination at other time points.
10. For the Screening assessment, a documented examination within six months of the Screening visit would also be acceptable but only when there was NO clinical change (e.g., decrease in visual acuity/visual field) since the last prior funduscopy. The end of treatment/early withdrawal assessment eye exam should be carried out by the investigator.
11. Height measured and body mass index calculated at Screening only. Weight, blood pressure, and heart rate (pulse); obtain blood pressure and pulse after sitting for at least 5 minutes.
12. All 12-lead ECGs to be performed before measurement of vital signs and collection of blood samples for laboratory testing. Subjects to be semirecumbent for 10 to 15 minutes before obtaining the ECG.
13. See Section 6.3.1 for hypoglycemic events criteria and reporting requirements. Subjects will be asked to report hypoglycemic events that occur between study visits in a diary.
14. Fasting is defined as no food or drink (except water) for at least 8 hours before blood draw.
15. Hematology to include complete blood count with red blood cell indices, white blood cell count differential, and platelet count.
16. 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, and phosphorus. Calculate estimated glomerular

filtration rate using the Modification of Diet in Renal Disease formula.

17. Fasting plasma glucose only.
18. Fasting plasma glucose, creatinine, alanine aminotransferase, total bilirubin, direct bilirubin, γ-glutamyltransferase, and alkaline phosphatase only.
19. Urinalysis to include specific gravity, pH, glucose, ketones, microalbumin, creatinine, blood, leukocyte esterase, and nitrites. (If warranted, a microscopic evaluation will be completed.)
20. Thyroid-stimulating hormone assessment at Screening only. Free T4 (reflex) will be measured if TSH is above upper limit of normal.
21. Blood sample for genetic research can be collected at any time during the study after the genetics informed consent has been obtained and the subject has been randomly assigned to treatment group.
22. Urine pregnancy test for women of childbearing potential only and at any time that pregnancy is suspected.
23. If hepatitis C antibody is positive, an RNA polymerase chain reaction should be performed on the same sample to confirm the result.
24. As described in Section 3.1, an optional fasting HbA_{1c} value may be determined using a Metrika kit or other finger-stick procedure to provide an initial guide of subject eligibility for investigators.
25. If the HbA_{1c} value at Week -1 is not ≥7.0% and ≤9.0%, the assessment may be repeated on a weekly basis for a maximum of 2 additional weeks before randomization. The mean of all HbA_{1c} assessments (Week -1 plus the additional HbA_{1c} assessments) must be ≥7.0% and ≤9.0% for the subject to be eligible for randomization. Note: If a subject has confirmed (by a central laboratory) HbA_{1c} <7.0% and >9.0% at Week -1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure.
26. Subjects will have both fasting C-peptide and stimulated C-peptide testing. If the fasting C-peptide is <0.8 ng/mL (<0.26 nmol/L) but stimulated C-peptide 90 minutes after a standardized mixed meal is ≥1.5 ng/mL (≥0.5 nmol/L), the subject meets the C-peptide inclusion criterion.
27. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and free fatty acids.
28. Insulin glargine and insulin lispro will be dispensed during the Standardization Period at Visit 2 (Week -4) with additional dispensing at Visit 3 (Week -1) optional as needed to ensure adequate supply up to Visit 4 (Week 0). Dispense albiglutide, insulin glargine, and insulin lispro, as appropriate, according to randomization at Baseline/Randomization. See Section 5.7 for additional information regarding insulin usage after Week 26/Early Withdrawal.
29. For subjects randomly assigned to the albiglutide plus insulin glargine treatment group ONLY, reduce insulin lispro by 50% at Baseline/Randomization followed by complete (100%) discontinuation of insulin lispro at Week 4. No downtitration of insulin lispro occurs in the insulin glargine plus insulin lispro treatment group.
30. During the Standardization Period, adjust insulin glargine and insulin lispro, as required, in accordance with product labeling in the respective country and standard of care at the study center. During the Treatment Period, titrate insulin glargine and/or insulin lispro according to Table 3 and Table 4, respectively. Titration should be based on the mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of self-monitored blood glucose measurements.
31. Randomization to occur at the Baseline/Randomization visit.

11.2.2. Scheduled Telephone Visits

Table 6 Time and Events Table – Telephone Calls

Study Procedure	Week	Standardization		Treatment Perform telephone contact with subject at the time points specified (±3 days) and as required for appropriate management of the subject														Follow-up
		-3	-2	1	2	3	6	7	8	9	11	12	13	14	15	16	22	25	28
Efficacy assessments																			
Review glucose monitoring with subject[1]		x	x[2]	x	x	x	x	x	x	x[2]	x	x	x	x	x	x	x	x[2]	x
Review the need for dose titration[1]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Obtain daily insulin dose information[3]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety assessments																			
Review of concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for AEs/SAEs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycemic events[4]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

AE = adverse event; SAE = serious adverse event.

1. During the Standardization Period, adjust insulin glargine and insulin lispro in accordance with product labeling in the respective country and standards of care at the study center. During the Treatment Period, titrate insulin glargine and/or insulin lispro according to Table 3 and Table 4, respectively. Titration should be based on the mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements.
2. Remind subjects to perform 8-point SMBG profile assessment (before and 2 hours after breakfast, lunch, and dinner; at bedtime; and at 2 AM): 3 times in the week prior to the Baseline/Randomization visit (Visit 4, Week 0), Visit 7 (Week 10), and Visit 9 (Week 26).
3. Daily insulin use to be recorded in the subject diary, at least 3 days preceding study visit/telephone contact at Week 1 through Week 16, inclusive, and at Week 18, 22, 25, and 26.
4. See Section 6.3.1 for hypoglycemic events criteria and reporting requirements.

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Study Day

When study day is used for display or in comparisons the following algorithm will be used:

- **study day = date of assessment - date of first dose +1**, if date of assessment ≥ first dose date
- **study day = date of assessment - date of first dose**, if date of assessment < first dose date.

Note that the date of first dose is Day 1 and the day before the date of first dose is Day -1 (there is no Day 0).

11.3.2. Visit Slotting Algorithm

For all safety and efficacy parameters to be summarized or analyzed by visit, data records will be slotted to one of the protocol specified visits using the following algorithm:

a) Determine the therapy period and study day for all records using the algorithms from Appendix 4: Treatment Periods.

b) For all records (including unscheduled visit records, early withdrawal records and repeat visit records), use the therapy period and study day determined above with the slotting intervals in the Table Analysis Visit Windows below to slot the record to the appropriate analysis visit.

   - For records determined to be in the pre-therapy period, the Week -6 and Week -4 analysis visits will be based on the nominal visits recorded on the eCRF. The Week -1 and Baseline analysis visits will be assigned based on the study day slotting intervals as shown in the table below.
   - For records determined to be in the on-therapy period, use the study day with the slotting intervals in the table below to assign the records to the appropriate on-therapy analysis visit (Week 1 through Week 26).
   - For records determined to be in the post-therapy period, the study day will not be used for assigning the analysis visit. Instead, all post-therapy period records for subjects who complete randomized study treatment according to protocol will be assigned to the Week 30 post-therapy analysis visit. For subjects who terminate study treatment early, the follow-up analysis visit will be based on the nominal visit recorded on the eCRF. All other post-therapy period records for subjects who terminate study treatment early will be assigned to the 4 Week Follow-up analysis visit.

11.3.3. Early Withdrawal Assessment

For subjects who are withdrawn early, handling of efficacy endpoint results from end-of- treatment (EOT) visit will be based on the elapsed time between the EOT visit and the recorded last dose date in the study per CRF. Specifically:

- If the EOT visit is > 14 days since last dose, and the visit falls in the follow-up visits window, the results will be treated as follow-up results.
- If the EOT visit is >14 days since last dose, but the visit does not fall in the follow-up visit window, the results will not be used for analysis purposes, but will be listed in the data listing.
- If the EOT visit is at ≤ 14 days since last dose, the assessment is a valid assessment for efficacy analysis. The EOT result will be assigned to a scheduled visit based on the slotting algorithm. If an assessment already exists for the scheduled visit where the EOT is assigned, the assessment closest to the target study day for the visit will be used for analysis.

For safety endpoints, the EOT result will be assigned to a scheduled visit based on the slotting algorithm.

11.3.4. Analysis Visit Windows

Table - Analysis Visit Windows

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Week -6	-42	Visit = " SCREENING"
Week -4	-28	Visit = " STANDARDIZATION 1"
Week -1	-7	Visit = " STANDARDIZATION 4"
Baseline (Week 0)	1	Visit = " BASELINE"
Week 4	29	2 to 32 days
Week 5	36	33 to 53 days
Week 10	71	54 to 99 days
Week 18	127	100 to 155 days
Week 26 (End of Treatment Visit)*	183	Albiglutide arm: 156 to (last dose date + 25 days) Lispro arm: 156 to last dose date
Week 30**	211	For subjects completed study Albiglutide arm: >Last dose date + 25 days Lispro arm: >Last dose date
4 Week Follow-up Visit**	Last dose date + 35 days***	For subjects didn't complete study Albiglutide arm: >Last dose date + 25 days Lispro arm: >Last dose date

* Week 26 is the end of treatment visit for those subjects completing the study per-protocol. For subjects who withdraw early from active treatment, the end of treatment visit will be assigned to an analysis visit based on the visit slotting algorithm using study day and therapy phase.
** Week 30 is the 4 week post-treatment follow-up visit for those subjects completing the study per-protocol. The 4 Week Follow-up Visit is the 4 week post-treatment follow-up visit for those subjects who withdraw early from active treatment. Both visits will be assigned based on the visit slotting algorithm using therapy phase.
*** The target study day for the 4 Week Follow-up Visit for subjects who withdraw early from active treatment is set to be 5 weeks (35 days) after last dose to correspond with the timing of the 4 week post-treatment follow-up for subjects completing the study per-protocol (where last dose is at Week 25 and the follow-up visit is at Week 30).

For parameters which were not scheduled to be collected at all visits, the all-inclusive visit intervals defined for all visits (that is, the visit window table above) will still be used to slot records. However, if a value is slotted to a visit unscheduled for a parameter, it will not be summarized (and not be included in the efficacy datasets) but will be included in data listings.

For analyses on the prescribed insulin dose, the total number of weekly insulin injections and SMBG profile, visit and visit dates recorded on the eCRF are used for analysis because a specific visit date is needed to calculate the analysis values.

11.4. Appendix 4: Treatment Periods

For classifying AEs (including hypoglycemic events), the therapy periods will be defined as:

- **Pre-therapy:** The onset date of the AE is before the start date of randomized study medication. If the onset date of the AE is on the start date of randomized study medication, the AE will be considered as on-therapy.
- **On-therapy:** The onset date of the AE is on or after the start date of randomized study medication, and within last dose date plus 25 days in the albiglutide arm or within the last dose date in the lispro arm.
- **Post-therapy:** The onset date of the AE is more than 25 days after the last dose date in the albiglutide arm or after the last dose date in the lispro arm.

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

- **Pre-therapy:** The assessment date is on or before the start date of randomized study medication.
- **On-therapy:** The assessment date is after the start date of randomized study medication, and within last dose date plus 25 days in the albiglutide arm or within the last dose date in the lispro arm.
- **Post-therapy:** The assessment date is more than 25 days after the last dose date in the albiglutide arm or after the last dose date in the lispro arm.

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. Note that if the AE stop date is present, the imputed start date will always be on or prior to the stop date.

For the subjects in the insulin lispro + insulin glargine arm, the first drug dispense date recorded on eCRF after randomization is considered the starting date of treatment period. For the last dose date, it will be derived based on the last visit date. The last dose date will be Week 30 follow-up visit date for subject who completed the study, or the 4-week follow-up visit/end of study visit date for subjects who withdrew early.

For the subjects in the albiglutide + insulin glargine arm, the starting and last dose date will be derived based on the actual dose date of albiglutide in the exposure data set.

11.5. Appendix 5: Derived and Transformed Data

11.5.1. Change from Baseline

The baseline value for an assessment is defined as the last available non-missing value prior to the first dose of the randomized treatment. Change from Baseline is defined as the postbaseline value minus the baseline value for the given assessment.

11.5.2. Body Mass Index Calculation

Body mass index (BMI) will be calculated as follows:

$$\text{BMI} = \frac{\text{weight (kg)}}{[\text{height (m)}]^2}$$

11.5.3. Total Person Time on Treatment

The total person time on albiglutide treatment (in years) is defined as the total time on study medication between the time of the last dose date and the first dose date plus 26 days (to account for the long half-life of albiglutide) day and then divided by 365.25 days/year. For insulin lispro, it defined as the duration of study drug exposure (defined as the total time between the last dispensed dose date of randomized treatment and the first dose date of randomized treatment plus 1 day) divided by 365.25 days/year.

11.5.4. AE (Event) Density and Incidence Rate

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. The incidence rate for an AE will be calculated as the number of subjects experiencing that AE within a given period divided by the total person time on treatment (in years) of subjects at risk at the beginning of the same period.

To enhance the data presentation and to aid comparison between treatment groupings, all AE densities and all incidence rates of AEs will be presented per 100 person-years (by multiplying the above defined statistics by 100).

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

11.6.1. Premature Withdrawal

The reasons for subjects not completing the treatment period will be recorded as detailed in Section 4.5 of the protocol. Subjects who discontinue active participation in the study will no longer receive the randomized study medication. Immediately upon discontinuation from active participation in this study, these subjects should complete the early withdrawal assessments and return 4 weeks later for the follow-up assessments.

The reasons for subjects not completing the study will be recorded. Subjects who are withdrawn will not be replaced.

Per the protocol, insulin lispro may be re-introduced after Week 8 for subjects in the albiglutide treatment group, following a standardized, stepwise approach. Efficacy and safety assessments after the re-introduction of lispro will be included in the statistical analysis as is, without special handling.

11.6.2. Missing Date Imputation

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 a completely missing start date, the start date will be assumed to be prior to date of the first administration of study drug.

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 considered as ongoing.

For AE date imputation this rule will be followed but will be more conservative in nature consistent with the therapy phase (see Appendix 4: Treatment Periods for details).

Since 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.

11.6.3. Sensitivity Analysis on the Primary Efficacy Endpoint

Missing data are not explicitly imputed in the primary MMRM analysis; 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.

The sensitivity of the results of analysis to the method of handling missing values will be investigated, especially if the number of missing values is substantial or if the characteristics of missing values differ between treatment groups.

11.6.3.1. Extent of Missing Primary Analysis Data Endpoint

Missing data is expected to arise mainly from subjects missing complete visits. The amount of missing data for those baseline covariates included in the statistical analysis is expected to be none or at worst minimal. If it should occur, that subject will effectively be lost to analysis. Missing data for HbA_{1c} between two non-missing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment will be withdrawn from the study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA_{1c} value at Week 26 is missing (end of the study), the reason can be determined based on available data in these two locations. The reason for missing data can be classified as follows: safety, procedural (including withdrawal of consent), or lack of efficacy.

11.6.3.2. Reasons for Withdrawal

Reasons for withdrawal are assumed to fall into three broad categories:

- Procedural (i.e. lost to follow-up, investigator site closed, withdrew consent, protocol deviation, and investigator discretion that are not related to study treatment): In this case, it is expected that an assumption of missing at random (MAR) is appropriate for imputation of HbA_{1c} data after withdrawal.

- Safety (i.e. AE; subject reached protocol-defined stopping criteria; withdrew consent, protocol deviation, and investigator discretion that are related to study treatment): It is expected that, in most cases, any change in safety related to these reasons for withdrawal would have been captured prior to the subject withdrawing from the study. In Study GLP108486 (albiglutide versus lispro over background glargine), 5% of subjects in the albiglutide group and <1% in the lispro group had AEs leading to withdrawal of active treatment through Week 26. In the albiglutide group, the most common AE leading to withdrawal was injection site reaction (1.1%). Missing HbA_{1c} values after withdrawal due to safety concerns will be considered to possibly be missing not at random (MNAR).

- Lack of efficacy: In this treat-to-target study, a substantial number of cases of withdrawal due to lack of efficacy is not expected. Missing HbA_{1c} values after withdrawal due to lack of efficacy are considered to possibly be MNAR.

Sensitivity analyses will be performed for data missing due to safety concerns or due to lack of efficacy.

11.6.3.3. Handling of Missing Data

The impact of missing data will be explored, as outlined below, for the Full Analysis Population only.

Examination of Missing Data Patterns

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA_{1c} change from Baseline) that were completed at Weeks 4, 5, 10, 18 and 26.

1. Subjects who have Week 4 assessment only
2. Subjects who have assessments up to and including Week 5 only
3. Subjects who have assessments up to and including Week 10 only
4. Subjects who have assessments up to and including Week 18 only
5. Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 5 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from Baseline over time to assess the pattern of outcomes prior to withdrawal.

Sensitivity Analyses – Multiple Imputation

Sensitivity analyses using multiple imputation methods will be conducted. Firstly, missing data between two non-missing time points will be considered missing at random.

The following multiple imputation methods are proposed based on whether data are missing at random or not at random:

- All missing data assumed MAR: Imputation is based on means and variances-covariances from subjects in the same treatment group as the withdrawn subject and is comparable to MMRM. The main differences are that this approach uses separate covariance parameter estimation for each arm, and also separate regression parameters are estimated on baseline covariates within each arm. This more complex parameterization of the imputation model compared with the analysis model is valid. This approach will be used for all data missing post withdrawal. Here the estimand is one where after withdrawal all subjects progress in a similar way to those who remain in the trial. We expect the MMRM and this to give similar answers. If so, then it indicates any difference between the primary MMRM analysis and multiple imputation sensitivity analysis is due to the assumed effect modification and the assumed rates of HbA_{1c} increase after withdrawal, rather than anything to do with going from an MMRM approach to a multiple imputation approach.
- Missing due to lack of efficacy or due to safety concerns using last mean carried forward (LMCF), which is MNAR (Carpenter and Kenward (2013)) (Step 2

below). The imputed values based on LMCF will be then updated with an added delta using a constant rate of increase in HbA_{1c} change from Baseline is experienced by subjects following withdrawal from the study for lack of efficacy or due to safety concerns (Step 3 below). The MAR approach will be used for missing data due to procedural reasons. Sensitivity analyses using the LMCF approach will be performed using the following rates of HbA_{1c} increase: 0%/month, 0.1%/month, and 0.2%/month to explore the potential impact as in a tipping-point analysis. For each treatment group, these 3 rates will be assumed, resulting in 9 scenarios. The resulting treatment differences and associated P-values for non-inferiority will be tabulated against the varying rates of HbA_{1c} increase. This estimand is one where those who withdraw for lack of efficacy or for safety concerns are assumed to revert to an unstable treatment regimen with an increasing rate of HbA_{1c}.

For each imputation data set, an analysis of variance will be carried using Week 26 data, both actual and imputed, using the same covariates as in the primary analysis. Contrasts of interest will be estimated and then combined across imputations using standard multiple imputation rules.

The details of implementing the multiple imputation assuming MAR and the multiple imputation using the LMCF approach are the following:

- Step 1: Multiple Imputation under MAR ($\boldsymbol{K}$=100 times)
  - Run PROC MI for all subjects BY treatment group (specifying the options chain=multiple in the MCMC statement).
  - As a result 100 sets of mean vectors ($\boldsymbol{\mu}$) and variance-covariance matrices ($\sum$) for each treatment group are simulated from the posterior distribution.
  - Each of the above 100 simulated parameter sets leads to a separate imputed dataset, in which the missing values ($\mathbf{Y_2}$) for each subject are replaced by values drawn randomly from their conditional distribution given the observed values ($\mathbf{Y_1}$). This condition distribution ($\mathbf{Y_2/Y_1}$) is multinomial with mean $\boldsymbol{\mu_2 + \sum_{21} \sum_{11}^{-1} (Y_1 - \mu_1)}$ and variance-covariance matrix $\boldsymbol{\sum_{22} - \sum_{21} \sum_{11}^{-1} \sum_{12}}$. So, 100 imputed datasets are generated.
- Step 2: Multiple Imputation using LMCF ($\boldsymbol{K}$=100 times)
  - For each imputed dataset from Step 1, update the imputed values (post-last observation) for only subjects who whtidraw due to lack of efficacy and safety concern as follows:
    - For each subject per treatment group, if there are any imputed values after the last observation ($\mathbf{Y}_{p,\,imp}$), first split the simulated mean vector ($\boldsymbol{\mu}$) into three parts: $\boldsymbol{\mu}_b$ (prior to last obs), $\boldsymbol{\mu}_{last}$ (last obs) and $\boldsymbol{\mu}_p$ (post last obs) and then update these imputed values as $\mathbf{Y}^*_{p,\,imp}=(\mathbf{Y}_{p,\,imp} - \boldsymbol{\mu}_p + \boldsymbol{\mu}_{last})$. Repeat for all subjects and for both treatment groups.
  - Repeat for the 100 imputed datasets from Step 1.
- Step 3: Multiple Imputation using added delta value ($\boldsymbol{K}$=100 times)
  - Calculate delta value for each subject at each visit post-last observation

        - Let γ_1 and γ_2 be the rates of HbA1c increase per month after the last observation for the Albiglutide and Insulin Lispro treatment group, respectively.
        - Let τ be the length of time between visits. Also, consider 1 month=4 weeks and determine τ using the visit week values. For example, time between visits Week 16 and Week 20 is 4 weeks (i.e. 1 month) and time between visits Week 16 and Week 26 is 10 weeks (i.e. 10/4=2.5 months).
        - For each subject and each visit post-last observation, a delta value will be derived according to the treatment group the subject was randomized to and time between the last observation visit and the present visit (τ). If the subject belongs to the Albiglutide treatment group, the delta value = $\gamma_1 \times \tau/4$; if the subject belongs to the Insulin Lispro treatment group, the delta value = $\gamma_2 \times \tau/4$.
    - For each updated imputed dataset from Step 2 increase the imputed values post-last observation by the corresponding delta values (per subject per visit post-last observation).
    - Repeat for the 100 imputed datasets from Step 2
- Step 4:
    - Perform Step 1 only for one scenario under MAR with 100 imputed datasets generated
    - Repeat Step 1, Step 2 and Step 3 for additional 9 scenarios using LMCF/delta method based on different rates of HbA1c increase for each treatment group
        - γ_1=0/month , γ_2=0/month
        - γ_1=0/month , γ_2=0.1/month
        - γ_1=0/month , γ_2=0.2/month
        - γ_1=0.1/month , γ_2=0/month
        - γ_1=0.1/month , γ_2=0.1/month
        - γ_1=0.1/month , γ_2=0.2/month
        - γ_1=0.2/month , γ_2=0/month
        - γ_1=0.2/month , γ_2=0.1/month
        - γ_1=0.2/month , γ_2=0.2/month
- Step 5: For each of the above 10 scenarios, apply ANCOVA analysis at Week 26 for each of the 100 imputed datasets and save the difference in LSmeans between treatment group and the associated standard error from each of the 100 analyses.
- Step 6: For each of the above 10 scenarios, combine the 100 set of analysis results using Rubin's rules (Rubin, 1987) via SAS PROC MIANALYZE. The treatment differences, confidence intervals and p-values will be estimated by MODELEFFECTS and STDERR statement. Use the degrees of freedom (EDF) you would have if the dataset were complete.

11.6.3.4. Sensitivity Analysis for Potential Data Integrity Issues

In case where there are data integrity issues, that could potentially impact the primary analysis outcome of the trial, we will perform a sensitivity analysis by excluding certain sites from the primary analysis.

One site in Poland (site ID = PPD has been stopped due to significant GCP concerns. A sensitivity analysis, with data from this site excluded, will be performed. For this, the planned primary analysis will be generated without data from this site. The results will be used to assess potential impact of data from this particular site on the primary analysis results.

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. Laboratory

Hematology			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Basophils	GI/L	None	None
Eosinophils	GI/L	None	None
Hematocrit	1	>0.1 decrease	>0.05 below LLN >0.04 above ULN
Hemoglobin	g/L	>25 g/L decrease	>20 g/L below LLN >10 g/L above ULN
Lymphocytes	GI/L	None	<0.5 x LLN
Monocytes	GI/L	None	None
Neutrophils	GI/L	None	<1 GI/L
Neutrophil Bands	GI/L	None	None
Platelets	GI/L	None	<80 GI/L >500 GI/L
Red Blood Cell Count	TI/L	None	None
Segmented Neutrophils	GI/L	None	<0.5 x LLN
White Blood Cell Count	GI/L	None	>1 GI/L below LLN >5 GI/L above ULN

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Albumin	g/L	None	>5 g/L above ULN or below LLN
Alkaline Phosphatase	U/L	None	>3 x ULN
ALT	U/L	None	>3 x ULN
AST	U/L	None	>3 x ULN
Bicarbonate (Carbon Dioxide Content)	mmol/L	None	<16 mmol/L > 40 mmol/L
Blood Urea Nitrogen	mmol/L	None	>2 x ULN
Calcitonin	pmol/L	None	>100
Calcium	mmol/L	None	<1.8 mmol/L

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
			>3.0 mmol/L
Chloride	mmol/L	None	None
Creatinine	umol/L	None	>159 umol/L
Direct Bilirubin	umol/L	None	>1.35 x ULN
Gamma Glutamyl Transferase	U/L	None	>3 x ULN
Glucose (fasting)	mmol/L	None	<3 mmol/L >22 mmol/L
Magnesium	mmol/L	None	<0.411 mmol/L >1.644 mmol/L
Phosphorus	mmol/L	None	>0.323 mmol/L above ULN or below LLN
Potassium	mmol/L	None	>0.5 mmol/L below LLN >1.0 mmol/L above ULN
Sodium	mmol/L	None	>5 mmol/L above ULN or below LLN
Total Bilirubin	umol/L	None	>1.5 x ULN
Total Protein	g/L	None	>15 g/L above ULN or below LLN
Uric acid	umol/L	None	>654 umol/L
Free Fatty Acids	mmol/L	None	None
HDL Cholesterol	mmol/L	None	None
LDL Cholesterol	mmol/L	None	None
Triglycerides	mmol/L	None	> 9.04 mmol/L
Total Cholesterol	mmol/L	None	None

Urinalysis	
Laboratory Test	**Potential Clinical Concern Value**
Urinalysis Albumin/Creatinine Ratio	>29 mg/g (>3.4 mg/mmol in SI units)

Liver Function Tests	
Laboratory Test	**Potential Clinical Concern Value**
ALT	≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN
AST	≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN
Total Bilirubin	≥ 1.5 x ULN ≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN

11.7.2. Vital Signs

Parameter	Units	Change from Baseline of Potential Clinical Concern	Potential Clinical Concern Value
Systolic BP	mmHg	Decrease >30 mmHg Increase >30 mmHg	<100 mmHg >170 mmHg
Diastolic BP	mmHg	Decrease >30 mmHg Increase >30 mmHg	<50 mmHg >110 mmHg
Heart rate	bpm	Decrease >30 bpm Increase >30 bpm	<50 bpm > 120 bpm

11.7.3. ECG

Parameter	Units	Change from Baseline of Potential Clinical Concern	Potential Clinical Concern Value
Heart Rate	bpm	None	Supine: < 50 or > 120
QRS interval	msec	Increase of > 25% when baseline QRS >100 msec Increase of > 50% when baseline QRS ≤100 msec	>200 msec
QTcF	msec	≥ 60 msec	≥500 msec
PR Interval	msec	Increase of > 25% when baseline PR >200 msec Increase of > 50% when baseline PR ≤200 msec	>300 msec

11.8. Appendix 8: Multicenter Studies and Definition of Geographic Region for Statistical Analyses

Clinical sites will be clustered by geographic region since the number of subjects per clinical site is expected to be rather small. Geographic regions will be defined based on geographic proximity, similarity of medical practice in diabetes, and number of subjects per region. Subjects per region will be constrained such that the region with the largest sample size is no more than 3 times that of the region with the smallest sample size. The clustering will be finalized after clinical site selection and randomization are complete.

Final classification of Geographic region for clinical sites:

- Region 1: United States and Canada;
- Region 2: Mexico;
- Region 3: Brazil;
- Region 4: Poland and Hungary;
- Region 5: Germany, France, Spain, Italy and United Kingdom;
- Region 6: Philippines, South Africa and Korea.

11.9. Appendix 9: Examination of Covariates, Subgroups & Other Strata

11.9.1. Strata and Covariates

The randomization for this study is stratified by the following baseline characteristics:

- HbA_{1c} at Screening (<8.0% versus ≥8.0%)
- Age at randomization (<65 years versus ≥65 years)
- Current use of metformin (metformin use versus no metformin use)

The primary analysis of HbA_{1c} change from Baseline will use a mixed-effect model with repeated measures (MMRM), which includes HbA_{1c} change from Baseline at all postbaseline visits as dependent variables; treatment, region, age category, current use of metformin, visit week, treatment-by-week interaction, and baseline HbA_{1c}-by-week interaction as fixed effects; baseline HbA_{1c} as a continuous covariate; and subject as a random effect. MMRM will only include non-missing observations therefore imputation will not be performed.

11.9.2. Examination of Subgroups

The primary efficacy endpoint will be analyzed for the following subgroups using a MMRM model described in Section 7.

- Baseline HbA_{1c} (<8.0%, ≥8.0%)
- Gender (male, female)
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- Age at randomization (<65 years, ≥65 years)
- Baseline BMI (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 to <35 kg/m^2, ≥35 kg/m^2)
- Region (Region 1, Region 2, Region 3, Region4, Region5, Region 6)
- Duration of Type II diabetes (< 8 years, >= 8 - <= 13 years, > 13 years)
- Current use of metformin (metformin use, no metformin use)
- Baseline FPG tertiles

11.10. Appendix 10: Multiple Comparisons & Multiplicity

A closed testing strategy will be implemented for the multiple inferential tests among the primary and key secondary endpoints to preserve overall family-wise Type I error rate of 0.05. The strategy involves pre-specification of test order [Koch, 1996].

The first test to be conducted is the primary efficacy analysis of HbA_{1c} change from Baseline at Week 26 on treatment comparison of albiglutide versus insulin lispro using non-inferiority testing. The comparison will be evaluated inferentially at the 1-sided 0.025 criterion significance level. If the non-inferiority of albiglutide is established, testing of superiority for the key secondary endpoints and the primary endpoint will proceed sequentially in a step-down manner at a 2-sided significance level of 0.05 in the following order:

1) Change from Baseline in body weight at Week 26

2) Prescribed total daily insulin dose at Week 26

3) Change from baseline in HbA_{1c} at Week 26

If a test for higher order endpoints above does not reach statistical significance, the results of statistical tests for lower order endpoints will not be interpreted.

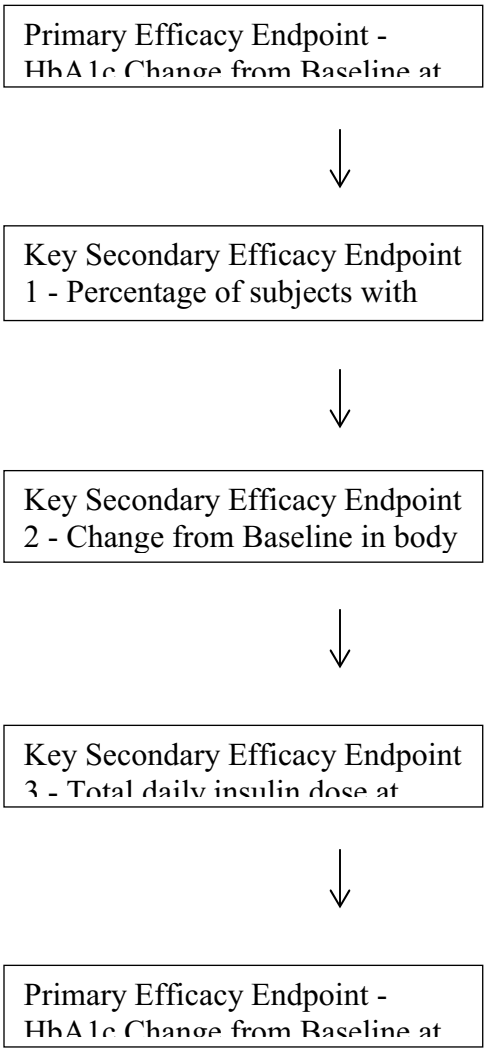
Note that for one of the key secondary endpoints listed in the protocol, proportion of subjects treated with once-weekly albiglutide that are able to discontinue insulin lispro at Week 4 and do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26, treatment comparison is not applicable as it is only defined for the Albiglutide + Insulin Glargine arm.

This is a treat-to-target study with the primary efficacy endpoint HbA_{1c} as the measurement. By the study design of treat-to-target, change from baseline in HbA_{1c} values in both treatment groups (Albiglutide + Insulin Glargine versus Insulin Lispro + Insulin Glargine), is expected to reach the target, and thus not expected to show a significant difference. Thus, testing of superiority for change from Baseline in HbA1c at Week 26 is considered lowest priority in the hierarchy of the multiple testing procedure.

Testing on other efficacy or exploratory endpoints, if applicable, will be considered exploratory and no multiplicity adjustment will be applied. Any secondary and exploratory endpoints that do not qualify for formal statistical testing will be analyzed and have results presented with confidence intervals and nominal p-values, if applicable.

The order of the testing strategy is shown in the diagram below.

Albiglutide + Insulin Glargine versus Insulin Lispro + Insulin Glargine


Primary Efficacy Endpoint - HbA1c Change from Baseline at
Key Secondary Efficacy Endpoint 1 - Percentage of subjects with
Key Secondary Efficacy Endpoint 2 - Change from Baseline in body
Key Secondary Efficacy Endpoint 3 - Total daily insulin dose at
Primary Efficacy Endpoint - HbA1c Change from Baseline at

11.11. Appendix 11: Model Checking and Diagnostics for Statistical Analyses

11.11.1. Model Checking and Diagnostics for Statistical Analyses

1. Example SAS code for the primary efficacy analysis of the primary endpoint (Model 1)

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS USUBJID TRT01PN REGION METFORMIN AGEGR1 AVISITN;
   MODEL CHG = BASE TRT01PN REGION METFORMIN AGEGR1 AVISITN
               TRT01PN*AVISITN BASE*AVISITN /DDFM =KR ;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS TRT01PN*AVISITN/SLICE=AVISITN CL DIFF;
   ESTIMATE 'Treatment difference at Week 26'
            TRT01PN 1 -1
            TRT01PN*AVISITN  0 0  0 0  1
                             0 0  0 0 -1 /CL ;
RUN;
```

2. Example SAS code for the supportive analysis – interaction terms- of the primary endpoint

For HbA1c (Baseline HbA1c category: HBGR1):

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS USUBJID TRT01PN REGION METFORMIN AGEGR1 AVISITN HBGR1;
   MODEL CHG = HBGR1 TRT01PN REGION METFORMIN AGEGR1 AVISITN
               TRT01PN*AVISITN HBGR1*AVISITN TRT01PN*HBGR1
               TRT01PN*HBGR1*AVISITN /DDFM =KR ;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS  TRT01PN*HBGR1*AVISITN/SLICE=AVISITN CL  DIFF;

   ESTIMATE 'Treatment difference at Week 26 for Baseline HbA1c
            Category < 8.0%'
            TRT01PN 1 -1
            TRT01PN*AVISITN  0 0  0 0 1   0 0  0 0  -1
            TRT01PN*HBGR1*AVISITN   0 0 0 0 0 0 0 0  1  0
                                    0 0 0 0 0 0 0 0 -1  0 /CL ;
RUN;
```

(or use the following statement to replace the 'LSMEANS' AND 'ESTIMATE' statements above:
SLICE HBR1*TRT01PN*AVISITN/SLICEBY(AVISITN='26') DIFF; and ODS table SLICETESTS to obtain p-value for the interaction at Week 26 (AVISITN=26).

For Age category, Metformin use or Region:

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS USUBJID TRT01PN REGION METFORMIN AGEGR1 AVISITN;
   MODEL CHG = BASE TRT01PN REGION METFORMIN AGEGR1 AVISITN
               TRT01PN*AVISITN BASE*AVISITN  TRT01PN*AGEGR1
               AVISITN*AGEGR1  TRT01PN*AGEGR1*AVISITN /DDFM =KR ;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS TRT01PN*AGEGR1*AVISITN /SLICE=AVISITN CL DIFF;

   ESTIMATE 'Treatment difference at Week 26 for Age category < 65'
            TRT01PN 1 -1
            TRT01PN*AVISITN        0  0  0 0 1   0 0  0 0  -1
            TRT01PN*AGEGR1*AVISITN 0  0 0 0  1 0 0 0  0  0
                                   0  0 0 0 -1 0 0 0  0  0 /CL ;

RUN;
```

Note: The contrasts may need to be adjusted for a different factor.

(or use the following statement to replace the 'LSMEANS' AND 'ESTIMATE' statements above:
SLICE HBR1*TRT01PN*AVISITN/SLICEBY(AVISITN='26') DIFF; and ODS table SLICETESTS to obtain p-value for the interaction at Week 26 (AVISITN=26).

3. Example SAS code for the by-subgroup analysis of the primary endpoint

Take by-FPG Tertiles as an example

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS USUBJID TRT01PN REGION METFORMIN AGEGR1 FPG_TTL AVISITN;
   MODEL CHG= BASE TRT01PN REGION METFORMIN AGEGR1 FPG_TTL
              AVISITN  TRT01PN*AVISITN BASE*AVISITN
              TRT01PN*FPG_TTL FPG_TTL*AVISITN
              TRT01PN*FPG_TTL*AVISITN /DDFM =KR ;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS TRT01PN*FPG_TTL*AVISITN/SLICE=AVISITN CL DIFF;
   ESTIMATE 'Treatment difference at Week 26 for 1st Baseline FPG
            Tertile'
   TRT01PN -1 1
   TRT01PN*AVISITN          0 0 0 0  1 0 0 0 0 -1
   TRT01PN*FPG_TTL*AVISITN  0 0 0 0  1 0 0 0 0  0
                            0 0 0 0  0 0 0 0 0 -1
                            0 0 0 0  0 0 0 0 0  0 /CL ;
RUN;
```

For Age category

Use the same SAS code for the supportive analysis on interaction terms.

For Baseline HbA1c category

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS USUBJID TRT01PN REGION METFORMIN AGEGR1 HBGR1 AVISITN;
   MODEL CHG= HBGR1 TRT01PN REGION METFORMIN AGEGR1 AVISITN
              TRT01PN*AVISITN HBGR1*AVISITN
              TRT01PN*HBGR1*AVISITN/DDFM =KR ;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS TRT01PN*AVISITN/SLICE=AVISITN CL DIFF;
   ESTIMATE 'Treatment difference at Week 26 for Baseline HbA1c
            <8.0%'
            TRT01PN -1 1
            TRT01PN*AVISITN        0 0 0 0  1 0 0 0 0 -1
            TRT01PN*HBGR1*AVISITN  0  0 0 0  1 0 0 0  0  0
                                   0  0 0 0 -1 0 0 0  0  0 /CL ;
RUN;
```

4. Example SAS code for key secondary efficacy endpoints Weight, Insulin dose etc (Model 2)

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS USUBJID TRT01PN REGION METFORMIN AGEGR1 AVISITN HBGR1;
   MODEL CHG= BASE TRT01PN HBGR1 REGION METFORMIN AGEGR1 AVISITN
              TRT01PN*AVISITN BASE*AVISITN /DDFM =KR ;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS TRT01PN*AVISITN/SLICE=AVISITN CL DIFF;
   ESTIMATE 'Treatment difference at Week 26'
            TRT01PN -1 1
            TRT01PN*AVISITN  0 0  0 0 -1
                             0 0  0 0  1 /CL ;
RUN;
```

Note: The contrasts may need to be adjusted for an endpoint that has a different visit scheme from that of HbA1c.

5. Example SAS code for analysis on FPG change from baseline by baseline FPG tertiles

```
ODS OUTPUT LSMeans= OUTLIBNAME.LSMeans SLICES= OUTLIBNAME.Diffs;
PROC MIXED DATA= INDATA;
   CLASS  USUBJID TRT01PN REGION METFORMIN AGEGR1 HBGR1 FPG_TTL
          AVISITN;
   MODEL CHG= FPG_TTL HBGR1 TRT01PN REGION METFORMIN AGEGR1
              AVISITN TRT01PN*AVISITN TRT01PN*FPG_TTL
              FPG_TTL*AVISITN TRT01PN*FPG_TTL*AVISITN /DDFM =KR;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   LSMEANS TRT01PN*FPG_TTL*AVISITN/SLICE=AVISITN CL DIFF;
   ESTIMATE 'Treatment difference at Week 26 for 1st Baseline FPG
            Tertile'
   TRT01PN -1 1
   TRT01PN*AVISITN          0 0 0 0  1 0 0 0 0 -1
```

```
   TRT01PN*FPG_TTL*AVISITN   0 0 0 0  1 0 0 0 0  0
                             0 0 0 0  0 0 0 0 0 -1
                             0 0 0 0  0 0 0 0 0  0 /CL ;
RUN;
```

5. Example SAS code for analysis on exposure-adjusted event rate with Poisson regression model

```
ODS OUTPUT LSMeans= Lsmeans Diffs=Diffs;
proc genmod data=INDATA;
   class USUBJID TRT01AN MCRIT2ML HBGR1 AGEGR1 METFMN CTRYGR1;
   model NUMEVT1=TRT01AN MCRIT2ML HBGR1 AGEGR1 METFMN CTRYGR1/
d=poisson offset=PYOFFSET;
   repeated SUBJECT=USUBJID /corrw covb type=exch;
   LSMEANS TRT01AN/ EXP ILINK E CL DIFF;
run;
```

11.12. Appendix 12: Sample Size Considerations

The primary hypothesis to be tested is that albiglutide plus insulin glargine (with or without metformin) will provide glycemic control (as measured by HbA_{1c} change from Baseline) noninferior to insulin lispro plus insulin glargine (with or without metformin) after 26 weeks of treatment in subjects with T2DM inadequately controlled on their current regimen of basal-bolus insulin therapy. If the null hypothesis of albiglutide inferiority is rejected, a test of superiority will be applied.

Approximately 794 subjects will be randomly assigned in a 1:1 ratio to 2 treatment groups. Eligible subjects will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and use of metformin (metformin use versus no metformin use). Assuming that 15% of subjects will be withdrawn early or will be lost to follow-up, approximately 337 subjects in each treatment group will complete 26 weeks of study assessments.

With 337 completed subjects in each of the 2 treatment groups, the study will have at least 90% power to reject the null hypothesis of inferiority for HbA_{1c} change from Baseline, assuming a non-inferiority margin of 0.3%, an expected treatment group difference of 0.0%, and a standard deviation of 1.2%, using a 2-sample, 1-sided t test with a test-wise significance level of 0.025.

If non-inferiority of albiglutide is established, superiority of albiglutide versus insulin lispro will be tested. Given the sample size of 337 completed subjects per treatment group and assuming a common standard deviation of 1.2, the minimum detectable difference in means between albiglutide and insulin lispro resulting in a significant test is 0.18, with a power of 50% and a type I error rate of 0.05.

11.13. Appendix 13: Abbreviations & Trade Marks

11.13.1. Abbreviations & Trade Marks

List of Abbreviations

AE	Adverse Event
AIC	Akaike information criterion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	β-human chorionic gonadotropin
CMH test	Cochran-Mantel-Haenszel test
CV	cardiovascular
dL	deciliter
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FA	full analysis
FPG	fasting plasma glucose
FSG	fasting serum glucose
g	gram
GCP	Good clinical practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HbA_{1c}	glycosylated hemoglobin
HFS-II	hypoglycemia fear survey-II
ICH	International Conference on Harmonisation
IU	international unit
kg	kilogram
L	liter
LMCF	last mean carried forward
m	meter
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mmol	millimole
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
PK	pharmacokinetic
PP	per-protocol
PT	Preferred Term
RAP	reporting and analysis plan
SAC	Statistical Analysis Complete
SAE	serious adverse event

SMBG	self-monitored blood glucose
SOC	System Organ Class
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TEAE	Treatment Emergent Adverse Event
TRIM-Diabetes	treatment-related impact measure for diabetes
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
HFS-II
Humalog
Lantus
MedDRA
TRIM-Diabetes

11.14. Appendix 14: List of Data Displays

11.14.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.46	N/A
Efficacy	2.01 to 2.701	2.01 to 2.92
Safety	3.01 to 3.348	3.01 to 3.71
Other Analysis		
Section	**Listings**	
ICH Listings	1 to 44	
Other Listings	101 to 170	

11.14.2. Mock Example Numbering

Non IDSL specifications will be referred as detailed below and where appropriate an example mock-up table is provided in a separate shell document:

Section	Figure	Table	Listing
Study Population			
Efficacy			
Safety			
Other Analysis			

NOTE:

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

11.14.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subjection Disposition, Demographics and Baseline Characteristics					
1.01	FA		Subject Disposition		
1.02			Summary of Study Enrollment and Reasons for Screening Failures and Standardization Failures		
1.03	FA		Reasons for Withdrawal from Study		
1.04	FA		Reasons for Discontinuing Study Treatment		
1.05	FA		Subject Status by Visit		
1.06	FA		Subjects Randomized across Sites		
1.07	FA		Inclusion/Exclusion Criteria Deviations		
1.08	FA		Significant Protocol Deviations		
1.09	FA		Demographics and Baseline Characteristics		
1.10	FA		Geographic Ancestry		
1.11	FA		Substance Use		
Medical History					
1.21	Safety		Medical and Family History Status		
1.22	Safety		Current and/or Past Cardiovascular Medical History		
1.23	Safety		Current and/or Past Diabetes Related Conditions		
1.24	Safety		Duration of Diabetes Disease History		
1.25	Safety		Current and/or Past Medical/Surgical Procedure History		
1.26	Safety		Current and/or Past Gastrointestinal Medical Conditions		
1.27	Safety		Current and/or Past Nephropathy (Including Microalbuminuria) and Kidney Injury History		

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.28	Safety		Current and/or Past Cancer History		
1.29	Safety		Current and/or Past Pneumonia Medical History		
1.30	Safety		Current and/or Past Skin Medical Conditions		
1.31	Safety		Current and/or Past Thyroid Medical History		
1.32	Safety		Current and/or Past Other Medical History		
Medications and Non-drug Therapies					
1.41	Safety		Prior Medications		
1.42	Safety		Concomitant Medications		
1.43	Safety		Post-therapy Medications		

11.14.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in HbA1c					
2.01	FA		Analysis of Change from Baseline in HbA_{1c} (%) at Week 26		
2.02	FA		Statistical Output Supporting the Analysis of Change from Baseline in HbA1c (%) at Week 26		
2.03	FA		Analysis of Selected Interaction Terms in MMRM Model for Change from Baseline in HbA1c (%) at Week 26		
2.04	FA		Statistical Output Analysis of Selected Interaction Terms in MMRM Model for Change from Baseline in HbA_{1c} (%) at Week 26		
2.05	Per-Protocol		Analysis of Change from Baseline in HbA1c (%) at Week 26 for Per-Protocol Population		
2.06	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Baseline HbA1c Category		
2.07	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Age Category at Randomization		
2.08	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Region		
2.09	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Current Use of Metformin		
2.10	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Gender		
2.11	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Race		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Ethnicity		
2.13	FA		Analysis of Change from Baseline in HbA_{1c} (%) at Week 26 by Baseline BMI Category		
2.14	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Duration of Type II Diabetes Category		
2.15	FA		Sensitivity Analysis of Change from Baseline in HbA1c (%) at Week 26		
2.16	FA		Examination of the Pattern of Missing HbA1c Values		
2.17	FA		Summary Statistics for HbA1c (%) by Visit		
2.18	FA		Analysis of Change from Baseline in HbA1c (%) over Time		
2.19	FA		Summary Statistics for HbA1c (%) by Visit and Baseline Fasting Plasma Glucose Tertiles		
2.20	FA		Analysis of Change from Baseline in HbA1c (%) at Week 26 by Baseline Fasting Plasma Glucose Tertiles		
2.21	FA		Sensitivity Analysis of Change from Baseline in HbA1c (%) at Week 26 Excluding All Data from One Site in Poland Closed Due to Significant GCP Concerns		
Subjects Treated with Once-Weekly Albiglutide That Are Able to Discontinue Insulin Lispro at Week 4 and Do Not Meet Prespecified Criteria for Severe, Persistent Hyperglycemia through Week 26					
2.31	FA		Proportion of Subjects Treated with Once-weekly Albiglutide That Are Able to Totally Replace Prandial Insulin without Re-introduction of Inuslin Lispro through Week 26		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.32	FA		Summary Characteristics of Albiglutide-treated Subjects by Prescribed Lispro Re-introduction Status (Albiglutide-treated Subjects Only)		
2.33	FA		Summary Statistics of Prescribed Total Lispro Daily Dose for Subjects Taking Re-introduced Lispro by Visit (Albiglutide-treated Subjects Only)		
2.34	FA		Summary of Number of Lispro (Prescribed) Injections per Day by Visit (Albiglutide-treated Subjects Only)		
Severe or Documented Symptomatic Hypoglycemia					
2.41	FA		Summary of Subjects with Severe or Documented Symptomatic Hypoglycemia through Week 26 by Baseline HbA1c Category, Age Category, Region, and Current Use of Metformin		
2.42	FA		Percentages of Subjects with Severe or Documented Symptomatic Hypoglycemia through Week 26		
2.43	FA		Percentages of Subjects with Severe or Documented Symptomatic Hypoglycemia through Week 26 – Excluding Early Withdrawals		
Change and Percent Change from Baseline in Body Weight					
2.51	FA		Analysis of Change from Baseline in Body Weight (Kg) by Visit		
2.52	FA		Analysis of Percent Change from Baseline in Body Weight (Kg) by Visit		
2.53	FA		Summary Statistics for Body Weight (Kg) by Visit		
2.54	FA		Summary Statistics for Percent Change from Baseline in Body Weight (Kg) by Visit		
Prescribed Insulin Dose and Number of Injections					

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.61	FA		Analysis of Prescribed Total Daily Insulin Dose (IU) at Baseline, Week 4, Week 5, Week 10, Week 18 and Week 26		
2.62	FA		Analysis of Body Weight Adjusted Prescribed Total Daily Insulin Dose (IU/Kg) at Baseline, Week 4, Week 5, Week 10, Week 18 and Week 26		
2.63	FA		Analysis of Prescribed Total Daily Basal Insulin (Insulin Glargine) Dose (IU) at Baseline, Week 4, Week 5, Week 10, Week 18 and Week 26		
2.64	FA		Analysis of Body Weight Adjusted Prescribed Total Daily Basal Insulin (Insulin Glargine) Dose (IU/Kg) at Baseline, Week 4, Week 5, Week 10, Week 18 and Week 26		
2.65	FA		Analysis of Prescribed Total Daily Bolus Insulin (Insulin Lispro) Dose (IU) at Baseline, Week 4, Week 5, Week 10, Week 18 and Week 26		
2.66	FA		Analysis of Body Weight Adjusted Prescribed Total Daily Bolus Insulin (Insulin Lispro) Dose (IU/Kg) at Baseline, Week 4, Week 5, Week 10, Week 18 and Week 26		
2.67	FA		Summary Statistics for Prescribed Insulin Dose		
2.68	FA		Summary Statistics for Total Number of Weekly Insulin Injections		
Change from Baseline in Fasting Plasma Glucose					
2.75	FA		Summary Statistics for Fasting Plasma Glucose (mmol/L) by Visit		
2.76	FA		Analysis of Change from Baseline in Fasting Plasma Glucose (mmol/L) by Visit		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.77	FA		Summary Statistics for Change from Baseline in Fasting Plasma Glucose (mmol/L) by Visit and Baseline Fasting Plasma Tertiles		
2.78	FA		Analysis of Change from Baseline in Fasting Plasma Glucose (mmol/L) at Week 26 by Baseline Fasting Plasma Tertiles		
2.79	FA		Statistical Output for the Analysis of Correlation between Fasting Plasma Glucose (mmol/L) and Fasting Serum Glucose (mmol/L) at Screening Visit		
Subjects Achieving HbA1c Target Response					
2.81	FA		Analysis of Proportion of Subjects Achieving HbA1c < 6.5% Response by Visit		
2.82	FA		Analysis of Proportion of Subjects Achieving HbA1c < 7.0% Response by Visit		
2.83	FA		Analysis of Proportion of Subjects Achieving HbA1c < 7.0% Response without Weight Gain at Week 26		
2.84	FA		Analysis of Proportion of Subjects Achieving HbA1c < 7.0% Response without Severe or Documented Symptomatic Hypoglycemia at Week 26		
2.85	FA		Analysis of Proportion of Subjects Achieving HbA1c < 7.0% Response without Weight Gain and without Severe or Documented Symptomatic Hypoglycemia at Week 26		
2.86	FA		Analysis of Proportion of Subjects Achieving HbA1c < 6.5% Response by Visit, Considering Missing HbA1c Values		
2.87	FA		Analysis of Proportion of Subjects Achieving HbA1c < 7.0% Response by Visit, Considering Missing HbA1c Values		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subjects Who Meet Prespecified Criteria for Severe, Persistent Hyperglycemia					
2.101	FA		Analysis of Proportion of Subjects Who Meet Prespecified Criteria for Severe, Persistent Hyperglycemia at Week 26		
2.102	FA		Kaplan-Meier Analysis of Time to Meeting Prespecified Criteria for Severe, Persistent Hyperglycemia		
2.103	FA		Summary Statistics for Proportion of Subjects Meeting Prespecified Criteria for Severe, Persistent Hyperglycemia		
Other Exploratory Endpoints					
2.201	FA		Summary Statistics for TRIM-Diabetes Questionnaire Total and Individual Domain Scores by Visit		
2.202	FA		Analysis of Change from Baseline in TRIM-Diabetes Questionnaire Total Score over Time		
2.203	FA		Analysis of Change from Baseline in TRIM-Diabetes Questionnaire Treatment Burden Score Over Time		
2.204	FA		Analysis of Change from Baseline in TRIM-Diabetes Questionnaire Daily Life Score over Time		
2.205	FA		Analysis of Change from Baseline in TRIM-Diabetes Questionnaire Diabetes Management Score over Time		
2.206	FA		Analysis of Change from Baseline in TRIM-Diabetes Questionnaire Compliance Score over Time		
2.207	FA		Analysis of Change from Baseline in TRIM-Diabetes Questionnaire Psychological Health Score over Time		
2.301	FA		Summary Statistics for HFS-II Questionnaire Worry Subscale Total Score by Visit		
2.302	FA		Analysis of Change from Baseline in HFS-II Questionnaire Worry Subscale Total Score over Time		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.401	FA		Summary Statistics for 8-Point Self-Monitored Blood Glucose (mmol/L) Profile by Visit		
2.402	FA		Summary Statistics for Daily Average Glucose Concentration from 8-Point Self-Monitored Blood Glucose (mmol/L) Profile by Visit		
2.403	FA		Analysis of Change from Baseline in Daily Average Glucose Concentration from 8-Point Self-Monitored Blood Glucose Concentration (mmol/L) Over Time		
2.501	FA		Analysis of Proportion of Subjects with <= 1 Kg Weight Gain at Week 26		
2.601	FA		Analysis of Proportion of Subjects Achieving HbA1c < 7.0% without Weight Gain and Without Hypoglycemia with Plasma Glucose <3.1 mmol/L (<56 mg/dL) Regardless of Symptoms at Week 26		
2.701	FA		Proportion of Subjects Treated with Once-weekly Albiglutide That Are Able to Totally Replace Prandial Insulin without Re-introduction of Inuslin Lispro and without Worsening HbA1c Control at Week 26		

11.14.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in HbA1c					
2.01	FA		Line Graph of Mean (+/- SE) of HbA1c (%) by Visit		
2.02	FA		Line Graph of Mean (+/- SE) of Change from Baseline in HbA1c (%) by Visit		
2.03	FA		Line Graph of LS Mean (+/- SE) of Change from Baseline in HbA1c (%) by Visit		
2.04	FA		Model-adjusted Change from Baseline in HbA1c (%) for Albiglutide vs. Insulin Lispro and 95% CI at Week 26		
2.05	FA		Line Graph of Mean of Change from Baseline in HbA1c (%) by Missing Data Patterns and Treatment		
Change and Percent Change from Baseline in Body Weight					
2.21	FA		Line Graph of Mean (+/- SE) of Body Weight (Kg) by Visit		
2.22	FA		Line Graph of Mean (+/- SE) of Change from Baseline in Body Weight (Kg) by Visit		
2.23	FA		Line Graph of LS Mean (+/- SE) of Change from Baseline in Body Weight (Kg)		
2.24	FA		Model-adjusted Change from Baseline in Body Weight (Kg) for Albiglutide vs. Insulin Lispro and 95% CI at Week 26		
2.25	FA		Line Graph of Mean (+/- SE) of Percent Change from Baseline in Body Weight (%) by Visit		
2.26	FA		Line Graph of LS Mean (+/- SE) of Percent Change from Baseline in Body Weight (%)		

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27	FA		Model-adjusted Percent Change from Baseline in Body Weight (%) for Albiglutide vs. Insulin Lispro and 95% CI at Week 26		
Prescribed Insulin Dose and Number of Injections					
2.41	FA		Line Graph of Mean (+/- SE) of Prescribed Daily Insulin Dose (IU) by Visit		
2.42	FA		Line Graph of Mean (+/- SE) of Body Weight Adjusted Prescribed Daily Insulin Dose (IU/Kg) by Visit		
2.43	FA		Line Graph of LS Mean (+/- SE) of Prescribed Daily Insulin Dose (IU) by Visit		
2.44	FA		Line Graph of LS Mean (+/- SE) of Body Weight Adjusted Prescribed Daily Insulin Dose (IU/Kg) by Visit		
2.45	FA		Model-adjusted Prescribed Total Daily Insulin Dose (IU) for Albiglutide vs. Insulin Lispro and 95% CI at Week 26		
Change from Baseline in Fasting Plasma Glucose					
2.61	FA		Line Graph of Mean (+/- SE) of Fasting Plasma Glucose (mmol/L) by Visit		
2.62	FA		Line Graph of Mean (+/- SE) of Change from Baseline in Fasting Plasma Glucose (mmol/L) by Visit		
2.63	FA		Line Graph of LS Mean (+/- SE) of Change from Baseline in Fasting Plasma Glucose (mmol/L) by Visit		
2.64	FA		Model-adjusted Change from Baseline in Fasting Plasma Glucose (mmol/L) for Albiglutide vs. Insulin Lispro and 95% CI at Week 26		
Meeting Prespecified Criteria for Severe, Persistent Hyperglycemia					
2.71	FA		Kaplan-Meier Plot of Time to Meeting Prespecified Criteria for Severe, Persistent Hyperglycemia		

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Endpoints					
2.81	FA		Line Graph of Mean (+/- SE) of Glucose Concentration from 8-Point Self-Monitored Blood Glucose (mmol/L) Profile by Visit and Time Points		
2.91	FA		Bar Plot for Proportion of Subjects Achieving HbA1c < 7.0% Response by Visit		
2.92	FA		Bar Plot for Proportion of Subjects Achieving HbA1c < 6.5% Response by Visit		

11.14.6. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure to Treatment					
3.01	Safety		Exposure to Treatment		
Treatment Compliance					
3.02	Safety		Treatment Compliance		
Adverse Events					
3.11	Safety		Overview of Adverse Events		
3.12	Safety		All On-therapy and Post-therapy Adverse Events		
3.13	Safety		Pre-therapy Adverse Events		
3.14	Safety		On-therapy Adverse Events		
3.15	Safety		Most Common On-therapy Adverse Events		
3.16	Safety		Post-therapy Adverse Events		
3.17	Safety		On-Therapy Adverse Events and the Information on Relation to Treatment		
3.18	Safety		On-therapy Adverse Events by Time of Onset With 12-Weeks Intervals		
3.19	Safety		On-therapy Non-serious Adverse Events		
3.20	Safety		On-Therapy Non-serious Adverse Events with Incidence of Preferred Term >=5% in Any Treatment Group and the Information on Relation to Treatment		
3.21	Safety		On-therapy and Post-therapy Adverse Events Related to Individual Study Treatment		
3.22	Safety		On-therapy Treatment-related Adverse Events		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.23	Safety		Post-therapy Treatment-related Adverse Events		
3.24	Safety		On-therapy and Post-therapy Treatment-related Adverse Events		
3.31	Safety		On-therapy and Post-therapy Adverse Events by Maximum Intensity		
3.32	Safety		On-therapy Adverse Events by Maximum Intensity		
3.33	Safety		Post-therapy Adverse Events by Maximum Intensity		
3.34	Safety		On-therapy and Post-therapy Adverse Events by Maximum Intensity		
3.41	Safety		Pre-therapy Serious Adverse Events		
3.42	Safety		On-therapy Serious Adverse Events		
3.43	Safety		On-Therapy Serious Adverse Events and the Information on Relation to Treatment		
3.44	Safety		Post-therapy Serious Adverse Events		
3.45	Safety		On-therapy Treatment-related Serious Adverse Events		
3.46	Safety		Post-therapy Treatment-related Serious Adverse Events		
3.47	Safety		On-Therapy Fatal Serious Adverse Events and the Information on Relation to Treatment		
3.48	Safety		On-Therapy Non-fatal Serious Adverse Events and the Information on Relation to Treatment		
3.51	Safety		On-therapy Adverse Events Leading to Permanent Discontinuation of the Randomized Study Drug		
3.52	Safety		On-therapy Adverse Events Leading to Withdrawal from Study		
AE of Special Interest					

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.61	Safety		Overview of On-therapy Adverse Events of Special Interest		
3.71	Safety		On-therapy Hypoglycemic Events by SAE Status, Relationship to Study Medication, and Withdrawal Status		
3.72	Safety		On-therapy Hypoglycemic Events by Treatment, Symptom, Severity, Intervention and Action Taken		
3.73	Safety		On-therapy Hypoglycemic Events by Blood Glucose Level		
3.74	Safety		On-therapy Daytime and Nocturnal Hypoglycemic Events		
3.75	Safety		On-therapy Hypoglycemic Events with Confirmed Home Plasma Glucose Monitoring <3.9 mmol/L and/or Requiring Third Party Intervention by Intervals for Time of Onset		
3.76	Safety		Analysis of Exposure-adjusted Incidence Rate of On-therapy Severe, Documented Symptomatic or Asymptomatic Hypoglycemic Events		
3.77	Safety		Analysis of Exposure-adjusted Incidence Rate of On-therapy Severe Hypoglycemic Events		
3.78	Safety		Analysis of Exposure-adjusted Incidence Rate of On-therapy Documented Symptomatic Hypoglycemic Events		
3.79	Safety		Analysis of Exposure-adjusted Incidence Rate of On-therapy Asymptomatic Hypoglycemic Events		
3.80	Safety		On-therapy Hypoglycemic Events Over Time by Onset Week		
3.91	Safety		On-therapy and Post-therapy Cardiovascular Adverse Events		
3.101	Safety		On-therapy and Post-therapy Thyroid Adverse Events Reported by the Investigator		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.102	Safety		On-therapy and Post-therapy Thyroid Adverse Events Identified by a Customized MedDRA Query		
3.111	Safety		Summary of Gastrointestinal Adverse Events		
3.112	Safety		On-therapy Gastrointestinal Adverse Events		
3.113	Safety		On-therapy Serious Gastrointestinal Adverse Events		
3.114	Safety		On-therapy Treatment-related Gastrointestinal Adverse Events		
3.115	Safety		On-therapy Gastrointestinal Adverse Events Leading to Permanent Discontinuation of Study Treatment before Scheduled End of Treatment Period		
3.116	Safety		On-therapy Gastrointestinal Adverse Events Over Time		
3.117	Safety		On-therapy Gastrointestinal Adverse Events by Onset Week		
3.118	Safety		Kaplan-Meier Analysis of Time to First Occurrence of On-therapy Gastrointestinal Adverse Event		
3.119	Safety		On-therapy Nausea Over Time		
3.120	Safety		On-therapy Diarrhea Over Time		
3.121	Safety		On-therapy Vomiting Over Time		
3.122	Safety		On-therapy Nausea or Vomiting Over Time		
3.131	Safety		On-therapy and Post-therapy Potential System Allergic Reactions Identified by the Investigator		
3.132	Safety		On-therapy and Post-therapy System Allergic Reactions Identified by a Customized MedDRA Query		
3.133	Safety		Kaplan-Meier Analysis of Time to First Occurrence of On-therapy Systemic Allergic Reaction Reported by the Investigator		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.134	Safety		Kaplan-Meier Analysis of Time to First Occurrence of On-therapy Systemic Allergic Reaction Identified by a Customized MedDRA Query		
3.141	Safety		On-therapy and Post-therapy Injection Site Reactions		
3.142	Safety		Kaplan-Meier Analysis of Time to First Occurrence of On-therapy Injection Site Reaction		
3.143	Safety		On-therapy Injection Site Reaction Over Time		
3.144	Safety		Summary Characteristics of On-therapy Injection Site Reactions Identified by the Investigator		
3.151	Safety		On-therapy and Post-therapy Liver Events Identified by a Customized MedDRA Query		
3.161	Safety		On-therapy and Post-therapy Pancreatitis and Pancreatic Cancer		
3.162	Safety		On-therapy and Post-therapy Adjudicated Pancreatitis Events		
3.171	Safety		On-therapy and Post-therapy Atrial Fibrillation and Atrial Flutter Adverse Events		
3.181	Safety		On-therapy and Post-therapy Pneumonia Adverse Events Reported by the Investigator		
3.182	Safety		On-therapy and Post-therapy Pneumonia Adverse Events Identified by a Customized MedDRA Query		
3.191	Safety		On-therapy and Post-therapy Diabetic Retinopathy Adverse Events		
3.201	Safety		On-therapy and Post-therapy Appendicitis Adverse Events		
3.211	Safety		On-therapy and Post-therapy Malignant Neoplasm Adverse Events Identified by a Customized MedDRA Query		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Labs					
3.221	Safety		Change from Baseline in Hematology by Visit		
3.222	Safety		Change from Baseline in Chemistry by Visit		
3.223	Safety		Hematology Values of Clinical Concern by Visit		
3.224	Safety		Chemistry Values of Clinical Concern by Visit		
3.225	Safety		Liver Function Tests of Clinical Concern by Visit		
3.226	Safety		Shift in Hematology by Visit		
3.227	Safety		Shift in Chemistry by Visit		
3.228	Safety		Urinalysis by Visit		
3.229	Safety		Change from Baseline to Week 26 in Urine Albumin/Creatinine Ratio (mg/mmol)		
3.230	Safety		Shift in Urine Albumin/Creatinine Ratio From Baseline to Week 26		
Vital Signs					
3.231	Safety		Change from Baseline in Vital Signs by Visit		
3.232	Safety		Vital Signs of Clinical Concern by Visit		
3.233	Safety		Shift in Vital Signs of Clinical Concern by Visit		
ECGs					
3.341	Safety		Change from Baseline in ECG Values by Visit		
3.342	Safety		ECG Values of Clinical Concern by Visit		
3.343	Safety		Overall ECG Interpretations by Visit		
3.344	Safety		Shift in ECG Values of Clinical Concern from Baseline to Week 26		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.345	Safety		ECG QTcF and QTcB Results by Category		
3.346	Safety		ECG QTcF and QTcB Change from Baseline by Category		

11.14.7. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.01	Safety		On-therapy Hypoglycemic Events Over Time		
3.11	Safety		On-therapy Gastrointestinal Adverse Events Over Time		
3.12	Safety		Kaplan-Meier Plot of Time to First Occurrence of a Gastrointestinal Adverse Event over Time		
3.13	Safety		On-therapy Nausea Over Time		
3.14	Safety		On-therapy Diarrhea Over Time		
3.15	Safety		On-therapy Vomiting Over Time		
3.16	Safety		On-therapy Nausea or Vomiting Over Time		
3.31	Safety		Kaplan-Meier Plot of Time to First Occurrence of a Systemic Allergic Reaction Reported by the Investigator		
3.32	Safety		Kaplan-Meier Plot of Time to First Occurrence of a Systemic Allergic Reaction Identified by a Customized MedDRA Query		
3.41	Safety		Kaplan-Meier Plot of Time to First Occurrence of an Injection Site Reaction		
3.42	Safety		On-therapy Injection Site Reaction Over Time		
Labs					
3.51	Safety		Line Graph of Mean (+/- SE) Results for Hematology Parameters		
3.52	Safety		Line Graph of Mean (+/- SE) Results for Chemistry Parameters		

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.53	Safety		Line Graph of Mean (+/- SE) Change from Baseline Results for Hematology Parameters		
3.54	Safety		Line Graph of Mean (+/- SE) Change from Baseline Results for Chemistry Parameters		
3.55	Safety		Line Graph of Mean (+/- SE) Urine Albumin/Creatinine Ratio		
3.56	Safety		Scatter Plot of Urine Albumin/Creatinine Ratio		
Vital Signs					
3.61	Safety		Line Graph of Mean (+/- SE) of Vital Sign Parameters		
3.62	Safety		Line Graph of Mean (+/- SE) Change from Baseline in Vital Sign Parameters		
ECGs					
3.71	Safety		Line Graph of Mean (+/- SE) ECG Results over Time		

11.14.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1	FA		Vital Signs of Clinical Concern		
2	FA		ECG Values of Clinical Concern		
3	FA		Serious Adverse Events		
4	FA		Fatal Adverse Events		
5	FA		Serious Non-fatal Adverse Events		
6	FA		Adverse Events Leading to Withdrawal from Study		
7	FA		Adverse Events Leading to Permanent Discontinuation of Study Drug		
8	FA		Hypoglycemic Events		
10	FA		Cardiovascular Events - Deep Vein Thrombosis/Pulmonary Embolism		
11	FA		Cardiovascular Events - Arrhythmias		
12	FA		Cardiovascular Events - Myocardial Infarction (MI)/Unstable Angina (UA)		
13	FA		Cardiovascular Events - Cerebrovascular Events/Stroke (CVA) and Transient Ischemic Attack (TIA)		
14	FA		Cardiovascular Events - Congestive Heart Failure		
15	FA		Cardiovascular Events - Peripheral Arterial Thromboembolism		
16	FA		Cardiovascular Events - Pulmonary Hypertension		
17	FA		Cardiovascular Events - Coronary Revascularization		
18	FA		Cardiovascular Events - Peripheral Revascularization		

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
19	FA		Cardiovascular Events - Valvulopathy		
20	FA		Pancreatitis Events		
26	FA		Thyroid Cancer/Nodules/Goiter		
30	FA		Customized MedDRA Query Identified Thyroid Adverse Events		
31	FA		Systemic Allergic Reactions Reported by the Investigator		
32	FA		Systemic Allergic Reactions Identified by Customized MedDRA Query		
33	FA		Injection Site Reactions		
35	FA		Liver Events Identified by a Customized MedDRA Query		
36	FA		Atrial Fibrillation/Flutter		
37	FA		Pneumonia Reported by the Investigator		
38	FA		Pneumonia Reported Identified by a Customized MedDRA Query		
39	FA		Diabetic Retinopathy		
40	FA		Appendicitis		
41	FA		Malignant Neoplasm		
42	FA		Hematology Values of Clinical Concern		
43	FA		Chemistry Values of Clinical Concern		
44	FA		Liver Function Test Results of Clinical Concern		

11.14.9. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
101	FA		Randomized Allocation to Treatment		
102	FA		Subject Disposition		
103	FA		Reasons for Withdrawal from Study		
104	FA		Reasons for Discontinuing Study Treatment		
105			Reasons for Screening Failures and Standardization Failures		
106	FA		Subject Visits		
107	FA		Inclusion/Exclusion Criteria Deviations		
108	FA		Protocol Deviations		
109	FA		Major Protocol Deviations		
110	FA		Analysis Populations		
111	FA		Demographics and Baseline Characteristics		
112	FA		Geographic Ancestry		
113	FA		Substance Use		
115	FA		Cardiovascular Medical History		
116	FA		Diabetes Related Conditions		
117	FA		Diabetes Disease History		
118	FA		Medical/Surgical Procedure History		
119	FA		Gastrointestinal Medical Conditions		
120	FA		Nephropathy (Including Microalbuminuria) and Kidney Injury History		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
121	FA		Diabetic Retinopathy History		
123	FA		Cancer History		
124	FA		Pneumonia Medical History		
125	FA		Skin Medical Conditions		
126	FA		Thyroid Medical History		
127	FA		Thyroid Cancer History		
129	FA		History Benign Thyroid Conditions		
131	FA		Thyroid Cancer Family History		
132	FA		Pancreatitis Family History		
133	FA		Pancreatitis Cancer Family History		
134	FA		Other Medical History		
135	FA		Hypersensitivity - Past Medical Conditions		
136	FA		Prior and Concomitant Medications		
137	FA		Albiglutide Administration and Compliance		
138	FA		Albiglutide Accountability		
139	FA		Insulin Glargine Accountability and Compliance		
140	FA		Insulin Lispro Accountability and Compliance		
145	FA		HbA1c (%)		
146	FA		Stratifying Factors Used in MMRM Models		
147	FA		Subgroup Values Used in Subgroup Analyses		
149	FA		Weight (Kg)		
150	FA		Insulin Surveillance		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
151	FA		Fasting Plasma Glucose (mmol/L)		
152	FA		TRIM-Diabetes (TRIM-D) Questionnaire Scores		
153	FA		Hypoglycemia Fear Survey-II (HFS-II) Questionnaire Worry Subscale Scores		
154	FA		8-Point Self-Monitored Blood Glucose (SMBG) Profile		
155	FA		Adverse Events		
156	FA		Treatment Emergent Adverse Events		
157	FA		Hematology Laboratory Evaluations		
158	FA		Chemistry Laboratory Evaluations		
159	FA		Urinalysis Laboratory Evaluations		
160	FA		Urine Albumin/Creatinine Ratio		
161	FA		Vital Signs		
162	FA		ECG Values		
163	FA		Overall ECG Interpretations		
164	FA		Pregnancies		
165	FA		Liver Events Information		
166	FA		Liver Biopsy		
167	FA		Liver Imaging		
168	FA		Other Medical/Surgical Procedures		
170	FA		Other Lab Results at Screening		

11.14.10. Mock Shells for Data Displays