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

Title	:	Reporting and Analysis Plan for A Repeat-dose Study in Subjects with Type 2 Diabetes Mellitus to Assess the Efficacy, Safety, Tolerability and Pharmacodynamics, of Albiglutide Liquid Drug Product
Compound Number	:	GSK716155
Effective Date	:	14-JUL-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200952.
- This RAP is intended to describe the planned efficacy (primary, secondary and exploratory) and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the content of the final Statistical Analysis Complete (SAC) Deliverable.

Author's Name and Functional Area:

PPD	PPD	14-JUL-2017
Senior Biostatistician, PPD	Biostatistics Team Lead, PPD	

Approved by:

PPD	14-JUL-2017
Principal Statistician, Clinical Statistics, R&D Projects Clinical Platforms & Sciences, GlaxoSmithKline	

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This study will evaluate the efficacy, safety, tolerability and pharmacodynamics (PD) response of albiglutide liquid drug product relative to the commercial lyophilized drug product in subjects with type 2 diabetes mellitus (T2DM) failing to achieve optimal glycemic control on their current regimen of diet and exercise or stable dose of metformin. Specifically, potential for immunogenicity (e.g. incidences of anti-drug antibodies [ADA]) and injection site reactions (ISRs) will be evaluated as part of the overall safety assessment in this study.
Protocol	• This RAP is based on the protocol amendment [(Dated: 26/MAY/2016) of study GSK200952 (GSK Document No. : 2014N210004_02] and eCRF Version 2.
Primary Objective	• To evaluate the efficacy of albiglutide liquid product as measured by glycated hemoglobin (HbA1c) change from baseline at Week 26.
Primary Endpoint	• Change from baseline in HbA1c at Week 26
Study Design	• This is a phase III, randomized, double-blind, multicenter, parallel-group, repeatdose, study of 26 weeks duration to evaluate the efficacy, safety, tolerability and PD response of albiglutide liquid drug product relative to the commercial lyophilized drug product in subjects with T2DM. • The study will recruit subjects with T2DM who are failing to achieve optimal glycemic control on their current regimen of diet and exercise or stable dose of metformin. Subjects will continue on their current regimen for the duration of their participation in the study. • This study will comprise 3 study periods: screening (2 weeks), treatment (26 weeks) and for those subjects not entering the extension study a follow-up period (8 weeks). • At randomization, subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin). Subjects will be randomized in a 1:1 ratio to either Albiglutide liquid drug product administered by an auto-injector or Albiglutide lyophilized drug product administered by a pen-injector.
Planned Analyses	• Final Analysis: After all subjects have completed the planned 26 weeks of randomized study treatment and the subsequent follow-up phase if applicable, the final analysis for the clinical study report will be performed. At this time, the database will be frozen.
Analysis Populations	• Intent-to-Treat (ITT) Population • Safety Population • Per-Protocol (PP) Population • Pharmacokinetics (PK) Population
Hypothesis	• The primary hypothesis to be tested is that the liquid drug product will provide

Overview	Key Elements of the RAP
	glycemic control (as measured by HbA1c change from baseline) non-inferior to the lyophilized drug product for a period of 26 weeks of treatment in subjects with T2DM.
Primary Analyses	• The primary endpoint is the change from baseline in HbA1c at Week 26, which will be analyzed using a mixed-effect model with repeated measures (MMRM) in the intent-to-treat (ITT) population. MMRM will use all available data from Week 4 up to Week 26 after hyperglycemia rescue and discontinuation from investigational product. Imputation under the non-inferiority null hypothesis for missing data will be incorporated. Multiple imputations will be used to replace missing data of change from baseline of HbA1c at Week 26 for all subjects in both treatment arms as a first step, and then to make all the imputed values for the liquid drug product arm worse by the non-inferiority margin 0.4. Non-inferiority testing will be performed at a one-sided alpha of 0.025 and non-inferiority margin of 0.4%.
Secondary Analyses	• The evaluation of the safety and tolerability as assessed by immunogenicity and ISRs of albiglutide liquid drug product and the lyophilized drug product will be provided by reporting the event rates, and the associated 95% CI. • The overall general safety and tolerability of albiglutide liquid drug product versus lyophilized drug product will be evaluated in tabular and/or graphical format and summarized descriptively. • The secondary endpoint Fasting Plasma Glucose (FPG) change from baseline at Week 26 will be analyzed using MMRM without imputation. • To assess the PD effect of albiglutide over time for the secondary endpoints change from baseline in HbA1c and in FPG over time; MMRM models without imputation will be used. • Pharmacokinetics (PK) trough plasma concentration data will be summarized by treatment. No formal statistical analyses will be conducted.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the planned statistical analysis specified in the protocol amendment 2 (Dated: 26/MAY/2016) are outlined below.

- Primary and supportive analyses:
    - Protocol specified "The MMRM model via PROC MIXED will include HbA1c change from baseline at post-baseline scheduled visits up to Week 26 as dependent variables; treatment, region, age category, weight category, background antidiabetic therapy, visit week and treatment-by-week interaction; baseline HbA1c as a continuous covariate; and subject as a random effect".
    - Changes in the Reporting & Analysis Plan:
        - Week 1 visit is excluded from the MMRM due to small or zero change in HbA1c expected at Week 1 and the primary endpoint is change from baseline inHbA1c at Week 26. Inclusion of this visit in the MMRM model does not add much statistical efficiency, instead it likely leads to a non-positive definite estimated variance matrix and thus unstable estimate of treatment effect.
        - Baseline HbA1c-by-week interaction is added in the MMRM to allow for a more appropriate model fit by accounting for different coefficients of baseline at each post-baseline visit (Week 4, 8, 12, 16, 20 and 26) and thus avoid potential convergence issue due to insufficient model specification.

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

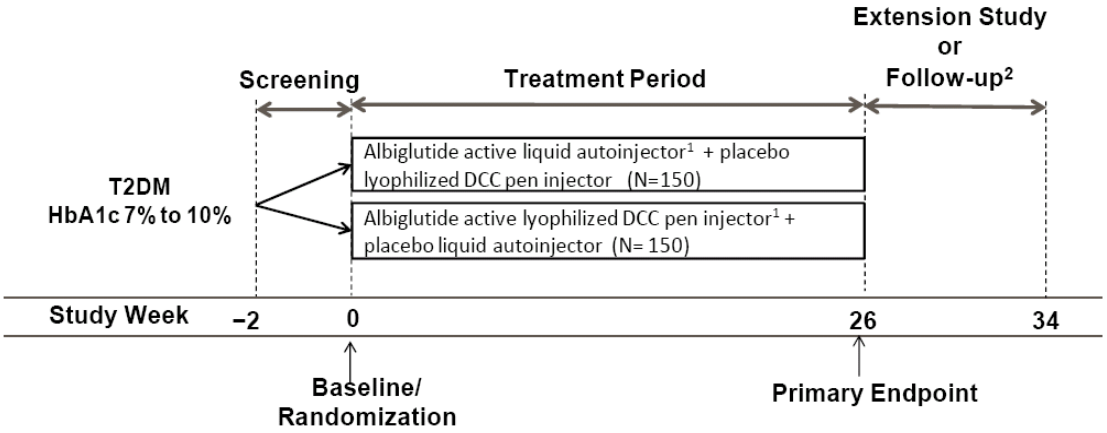
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of albiglutide liquid product as measured by glycated hemoglobin (HbA1c) change from baseline at Week 26.	• Change from baseline in HbA1c at Week26
Secondary Objectives	**Secondary Endpoints**
• To assess safety and tolerability of albiglutide specifically immunogenicity and ISRs.	• Adverse events (AEs) and serious AEs (SAEs), physical examinations, clinical laboratory evaluations, vital signs, and 12-lead electrocardiograms (ECGs).

Objectives	Endpoints
	• Anti-albiglutide antibody production and rates of ISRs over time.
• To evaluate the PD effect of albiglutide on fasting plasma glucose (FPG) change from baseline at Week 26.	• Change from baseline in FPG at Week 26
• To assess the PD effect of albiglutide over time	• Change from baseline in HbA1c over time • Change from baseline in FPG over time
• To evaluate trough PK concentrations of albiglutide following repeat dosing	• Trough concentrations of albiglutide

2.3. Study Design

2.3.1. Overview of Study Design and Key Features

Overview of Study Design and Key Features



DCC dual chamber glass cartridge

1. At baseline/randomization, albiglutide will be started at 30 mg once weekly with uptitration to albiglutide 50 mg once weekly at Week 4.
2. Follow-up visit only for those subjects who discontinued investigational product (see Section 5.5), were withdrawn from the study, or who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).

Design Features	• Randomized, double-blind, multicenter, parallel-group, repeat-dose study of 26 weeks duration
Dosing	• During the treatment period study treatment will be administered once weekly by subcutaneous (s.c.) injection in the abdomen, thigh, or upper arm. • Study personnel will administer study treatment at clinic visits. • Subjects will receive 30 mg of albiglutide for 4 weeks and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study. • Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is NOT permitted. If a subject experiences tolerability issues with the 50 mg dose then the subject may be withdrawn from the study at the discretion of investigator.
Treatment Assignment	• Randomized treatment assignment will be done via the Interactive Voice Response System (IVRS) and randomization will be implemented based on a sequestered fixed randomization schedule. • Approximately 300 subjects will be randomized for this study. Eligible subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin). Subjects will be randomized in a 1:1 ratio to either: 1. Albiglutide active liquid auto-injector + placebo lyophilized DCC pen injector; or, 2. Albiglutide active lyophilized DCC pen injector + placebo liquid auto-injector.
Interim Analysis	• No interim analysis is planned for this study.

2.3.2. Study Design

This is a phase III, randomized, double-blind, multicenter, parallel-group, repeatdose, study of 26 weeks duration to evaluate the efficacy, safety, tolerability and PD response of albiglutide liquid drug product relative to the commercial lyophilized drug product.

This study will comprise 3 study periods: screening (2 weeks), treatment (26 weeks) and for those subjects not entering the extension study a follow-up period (8 weeks).

The study will recruit subjects with T2DM who are failing to achieve optimal glycemic control on their current regimen of diet and exercise or stable dose of metformin. Subjects will continue on their current regimen for the duration of their participation in the study.

During the screening period, subjects will provide written informed consent and undergo procedures to determine eligibility for study participation. Screening will occur within 2 weeks of randomization.

At randomization, subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin). Subjects will be randomized in a 1:1 ratio to either:

- Albiglutide active liquid auto-injector + placebo lyophilized DCC pen injector;

or,

- Albiglutide active lyophilized DCC pen injector + placebo liquid auto-injector.

Study treatment will be administered once weekly by s.c. injection in the abdomen, thigh, or upper arm. Study personnel will administer study treatment at clinic visits. Subjects will receive 30 mg of albiglutide for 4 weeks and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study. Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is NOT permitted. If a subject experiences tolerability issues with the higher 50mg dose then the subject may discontinue investigational product (at the discretion of the investigator) and will be followed for safety and efficacy.

Subjects who completed the 26 week treatment period, did not discontinue investigational product, and meet all eligibility criteria may consent to participate in Study 204682, a 26 week extension study.

2.4. Statistical Hypotheses

The primary hypothesis to be tested is that the liquid drug product will provide glycemic control (as measured by HbA1c change from baseline) non-inferior to the lyophilized drug product for a period of 26 weeks of treatment in subjects with T2DM.

- The null hypothesis is that the difference in the mean change from baseline to Week 26 in HbA_{1c} between the liquid drug product and the lyophilized drug product is greater than the non-inferiority margin of 0.4%.

- The alternative hypothesis is that the difference in the mean change from Baseline to Week 26 in HbA_{1c} between the liquid drug product and the lyophilized drug product is less than or equal to the non-inferiority margin of 0.4%.
- The null 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 HbA1c change from baseline as the dependent variable; treatment, region (defined in Appendix 8: Multicenter), age category (<65 or >=65 years), weight category (<90 or >=90 kg), background antidiabetic therapy (diet and exercise or stable dose of metformin), visit week, treatment-by-week interaction and baseline HbA1c-by-week interaction as fixed effects; baseline HbA1c as a continuous covariate; and subject as a random effect. 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. If the upper bound of 1-sided 97.5% confidence interval is less than or equal to 0.4%, non-inferiority will be concluded.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.

3.2. Final Analyses

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

1. All subjects have completed the planned 26 weeks of study treatment or have completed participation in the study and the subsequent follow-up phase if applicable. For subjects who did not enter the extension study (Study 204682), they should complete the follow-up phase.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared.
3. All criteria for unblinding the randomization codes have been met.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat	• Comprise of all randomized subjects who receive at least one dose of study treatment and have a baseline assessment. • This population will be analysed according to randomly assigned treatment	• Efficacy
Safety	• Comprise of all enrolled subjects who receive at least one dose of study treatment. • This population will be analysed according to the treatment the subject actually received.	• Safety
Per-Protocol	• Comprise of all randomized subjects who complete study procedures through Week 26 and are compliant with the protocol. • This population will be analysed according to randomly assigned treatment. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population).	• Supportive analyses of the efficacy endpoints
Pharmacokinetic	• Subjects in the Safety population for whom a pharmacokinetic sample is obtained and analysed.	• PK

NOTES :

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

4.1. Protocol Deviations

- Significant protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, subject management or subject assessment) will be summarised by category and standard text description.
- Per-Protocol population is defined as all randomized subjects randomly assigned to treatment who complete study procedures on treatment through Week 26 and are compliant with the protocol. Significant deviations which result in exclusion from the Per-Protocol population will also be listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Study Deviation Rules document.

- Data will be reviewed prior to unblinding and freezing the database to ensure all significant deviations which may lead to exclusion from the Per-Protocol population are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and/or listings of protocol deviations.

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

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 data at Week 26 will be imputed. For the lyophilized drug product arm the imputation will be based on assumption of the missing at random (MAR) while for the liquid drug product arm the imputation will be performed assuming the worsening of 0.4 relative to what would be expected under MAR. Missing data handling and sensitivity analysis under different assumptions of missing mechanism 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
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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

Table 2Table 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	Data Display's Generated		
	Figure	Table	Listing
Randomization			
Randomization			Y
Subject Disposition			
Subject Disposition		Y	Y
Reasons for Screening 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 and Baseline Characteristics			
Demographics and Baseline Characteristics		Y	Y
Race & Racial Combinations		Y	Y
Substance use		Y	Y
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)		Y	Y
Concomitant Medication		Y	Y
Exposure and Treatment Compliance			
Exposure to Study Drug		Y	Y
Treatment Compliance		Y	Y

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

- Y = Yes display generated.

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

6.2. Disposition of Subjects

The number of subjects who were randomized and the number of subjects within each population (ITT, Safety, PP, PK) will be summarized for each treatment group. A summary of subjects randomized by geographic region, 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. Additionally, among subjects who completed the study the number and percentage of subjects who continued into the open-label extension study, and did not participate in the open-label extension study will be also summarized and tabulated.

Subject status by visit summary will be provided.

Subject disposition data will be listed as well. All disposition summaries will be based on the all randomized subjects.

6.3. Protocol Deviations

As described in Section 4.1, all significant protocol deviations, those leading to exclusion from PP population, and all inclusion/exclusion criteria deviations will be summarized and listed, separately.

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, and median, minimum, maximum). Categorical variables including age group (<65, ≥65 years), sex, race, ethnicity, baseline weight category (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin) will be summarized using numbers and percentages. Summaries will be presented by treatment group using the 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 safety 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 exposure to study drug will be presented by treatment group for the safety population. The duration of study drug exposure (in days) is defined as date of last dose of study drug - date of first dose of study drug + 1; missing doses will be ignored in this calculation. The total person time on study drug (in years) as defined in Appendix 5 will also be displayed for each treatment group.

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

6.6. Treatment Compliance

Study treatment (both active drug and placebo injector) will be administered to the subject by the site personnel in the clinic at each scheduled weekly visit from Week 0 (i.e. Baseline/Randomization), Week 1 through Week 25. At each scheduled weekly visit, study treatment administration status (Yes/No), date/time of dose administered (if Yes) and reason no dose administered (if No) will be recorded in the Exposure eCRF page.

Treatment compliance (in percentage) will be based on the Exposure eCRF page and calculated as total number of doses administered divided by total number of doses expected over all available scheduled visits on treatment. Treatment compliance will be summarized for all subjects, as well as for subjects who discontinue study treatment early and subjects who complete study treatment. Treatment compliance will be also categorized as < 80% and >=80%, and summarized descriptively by treatment group.

Individual subject compliance information will also be listed. All summaries will be performed using the safety population.

Acceptable overall compliance for IP (albiglutide liquid and lyophilized) in this study will be ≥80%.

6.7. 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 25 days after the last dose of randomized study drug, including those medications that started prior to randomization and continued into the treatment period. Post-therapy medications are those taken more than 25 days after the day of the last dose of randomized study drug.

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

6.8. Medical History

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

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

- pneumonia medical history
- skin medical conditions
- thyroid medical history, thyroid cancer history, benign thyroid medical conditions
- thyroid cancer family history
- pancreatitis family history
- pancreatic cancer family history
- other medical history
- other medical/surgical surgery

The number and percentage of subjects with current and/or past medical histories listed above will be reported 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.

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.

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 ITT 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

Endpoint/Parameter/ Display Type	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} at Week 26				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 maybe conducted to further support the evaluation and interpretation of the data.

7.1.1.1. Primary Analysis on Primary Efficacy Endpoint

The primary endpoint is the change from baseline in HbA1c at Week 26. The primary analysis of the primary endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the ITT Population. The primary analysis will include all HbA1c values collected at scheduled visits from Week 4 up to Week 26. This will include values after hyperglycemia rescue and discontinuation from investigational product. Imputation under the non-inferiority null hypothesis for missing data will be incorporated [Koch, 2008]. Multiple imputation assuming missing at random (MAR) will be used to replace missing data of change from baseline of HbA1c at Week 26 for all subjects in both treatment arms as a first step, and then to make all the imputed values for the liquid drug product arm worse by the non-inferiority margin 0.4.

Multiple imputation approach under MAR uses separate means and variance-covariance parameter estimation for each treatment arm (Carpenter and Kenward, 2013). Missing values for each subject will be imputed multiple times based on his or her own observed HbA1c change from baseline values available and also based on the estimated means and variance-covariance from the treatment group where that subject is randomized to. This approach will be used for all missing data at Week 26 due to any reason including, but not limited to lost to follow-up and withdrawl consent. The details of implementing this multiple imputation approach are the following:

- **Step 1a:** Missing values at Week 26 will be imputed 100 times via SAS PROC MI (specifying BY treatment group, using MCMC statement with the option chain = multiple, including baseline and all post-baseline scheduled visits up to Week 26). As a result, 100 imputed datasets will be generated. Note: Only imputed values at Week 26 will be retained while the imputed values at other visits will be dropped from the imputed datasets.
- **Step 1b:** For each of the 100 imputed datasets from Step 1 the imputed values at Week 26 for the liquid drug product arm will be increased by 0.4.
- **Step 2:** Apply MMRM analysis as specified below for each of the 100 imputed dataset and save LSmeans (standard error) for each treatment arm at Week 26 and difference in LSmeans between treatment groups (standard error) from each of the 100 analyses.
- **Step 3:** 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.

The MMRM model via PROC MIXED will include HbA1c change from baseline at post-baseline scheduled visits from Week 4 up to Week 26 as dependent variables; treatment, region (defined in Appendix 8: Multicenter), age category (<65 or >=65 years), weight category (<90 or >=90 kg), background antidiabetic therapy (diet and exercise or stable dose of metformin), visit week, treatment-by-week interaction and baseline HbA1c-by-week interaction as fixed effects; baseline HbA1c as a continuous covariate; and subject as a random effect. 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. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product.

The null hypothesis will be tested based on the 1-sided 97.5% confidence interval (with upper bound, equal to that of 2-sided 95% confidence interval) of the treatment difference at Week 26, which is estimated from the multiple imputation/MMRM (i.e. combined MMRM results from multiple imputation). If the upper bound of the confidence interval is less than or equal to 0.4%, non-inferiority will be concluded.

In addition, the observed HbA_{1c} and change from baseline HbA_{1c} will be summarized descriptively and presented graphically.

7.1.1.2. Supportive Analyses on Primary Efficacy Endpoint

- **Supportive analysis 1:**
  The primary endpoint change from baseline in HbA1c at Week 26 will be analysed using the same MMRM model as described in Section 7.1.1.1 but missing data are not explicitly imputed in this supportive analysis; although, there

is an underlying assumption that data is missing at random. All available scheduled post-baseline assessments from Week 4 up to Week 26 are utilized and, via modelling of the within subject correlation structure, the derived treatment difference at Week 26 is adjusted to take into account missing data. The MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) is considered appropriate as the supportive analyses, as it has been shown to give sensible answers to on-treatment questions in a range of practical situations [Siddiqui,2009].

The least squares means (and standard errors) of change from baseline in HbA_{1c} at Week 26 will be presented from the MMRM model. The least squares mean and the associated 1-sided 97.5% confidence interval (with upper bound, equal to that of 2-sided 95% confidence interval) of the treatment difference in change from baseline in HbA_{1c} will be reported at Week 26.

- **Supportive analysis 2:**

  Analysis excluding HbA1c data after hyperglycaemia rescue and discontinuation from study treatment will also be performed as supportive. It is not expected to have a substantial number of subjects who will require rescue and/or discontinue from study treatment and that number of subjects would be similar for both treatment arms. However, rescue medications given to subjects in this study may distort the estimates of the underlying treatment effect when HbA1c change from baseline values at Week 26 are associated with rescue medications. To assess the impact of rescue and pure drug effect, analysis of pre-rescue data will be performed. The MMRM model will be similar to the one as described in Section 7.1.1.1. Results of this analysis at Week 26 will supplement the primary analysis. No imputation will be conducted for this supportive analysis.

- **Supportive analysis 3**:

  The primary endpoint HbA1c change from baseline at Week 26 will be analyzed using the same MMRM model as described in Section 7.1.1.1 in the PP population as a supportive analysis. No imputation will be conducted for this 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 be examined by the following subgroups (also see Appendix 9) using the same multiple imputation/MMRM model approach for the primary analysis but also includes the subgroup- by-treatment-by-visit interaction term (as well as subgroup-by-treatment and subgroup-by-visit interaction terms) in the MMRM model step. The adjusted mean difference between treatment groups and associated 95% confidence interval for each level of the subgroup will be estimated from the combined MMRM results from the multiple imputations.

- Baseline HbA1c category (< 8% or >=8%)

- Region (USA – North, USA – South Atlantic, USA – South Central and USA - West)
- Age category (<65 or >=65 years)
- Weight category (<90 or >=90 kg)
- Background antidiabetic therapy (diet and exercise or stable dose of metformin)
- Gender (male or female)
- Race (white or non-white)
- Ethnicity (Hispanic or non-hispanic)
- Duration of diabetes category (<5, 5 to 10 or >10 years)

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 different methods of handling missing values. Detailed methodology is provided in Appendix 6: Premature Withdrawals & Handling of Missing Data.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Change from baseline in HbA1c at Week26
Model Specification
• **Multiple imputation**: Use PROC MI by specifying BY treatment group, using MCMC statement with the option chain = multiple and including baseline and all post-baseline scheduled visits up to Week 26. Then the imputed values at Week 26 for the liquid drug product arm will be replaced with the originally imputed values plus 0.4. • **MMRM model**: Change from Baseline in HbA_{1c} = Baseline HbA_{1c} + Treatment + Region + Age Category + Weight Category + Background Antidiabetic Therapy + Visit Week + Treatment-by-Visit Interaction + Baseline HbA1c-by-Visit Interaction. This model will be including all HbA1c values collected at scheduled visits from Week 4 up to Week 26 and will be performed for each imputation. • **Combining analysis results**: Use PROC MIANALYZE by applying the MODELEFFECTS and STDERR statement. The treatment differences, confidence intervals and p-values will be estimated by combining the multiple sets of MMRM results..
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The treatment difference at Week 26 and its 1-sided 97.5% confidence interval (or equivalently 2-sided 95% confidence interval) estimated from the combined MMRM results from multiple imputation. • Descriptive statistics for the observed HbA_{1c} and change from Baseline HbA_{1c} • Refer to Appendix 14 List of Data Displays

Supportive Statistical Analysis
• The primary endpoint will also be analyzed using the MMRM model above including all HbA1c values collected at scheduled visits from Week 4 up to Week 26. This would include values after post-hyperglycemia rescue and discontinuation from investigational product. No explicit data imputation will be performed. • The primary endpoint will also be analyzed using the MMRM model above excluding post-hyperglycemia rescue data and post discontinuation from study treatment data. No data imputation will be performed. • The primary endpoint will also be analyzed using MMRM model above in the Per-Protocol Population. No data imputation will be performed.
Model Specification
• Same MMRM model as for the primary analysis

By-Subgroup Statistical Analysis
• The subgroup analyses will be performed using the same multiple imputation/MMRM model approach except in the MMRM step a treatment by subgroup interaction term is added to the model. The subgroups include baseline HbA_{1c} category, region, age category (<65 or >=65 years), weight category (<90 or >=90 kg), background antidiabetic therapy (diet and exercise or stable dose of metformin), gender, race, ethnicity and duration of diabetes category. • 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 + Weight Category + Background Antidiabetic Therapy + Visit Week + Treatment-by-Visit + Baseline HbA1c-by-Visit Interaction + Subgroup (if not already in the model) + Subgroup-by-Treatment+ Subgroup-by-Visit + Subgroup-by-Treatment-by-Visit. • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses for SAS code

Sensitivity Statistical Analysis
• Refer to Appendix 6 Section 11.6.3.4: Sensitivity Analysis Under Missing Not At Random (MNAR)

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the ITT population.

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

Table 4 Overview of Planned Efficacy Analyses

	Stats Analysis			Summary		Individual	
Endpoint / Display Type	T	F	L	T	F	F	L
Change from baseline in FPG at Week 26	Y	Y		Y	Y		Y
Change from baseline in HbA1c over time	Y	Y		Y	Y		Y
Change from baseline in FPG over time	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.

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

FPG change from Baseline by visit will be analyzed using the similar MMRM model as described in Section 7.1.1.1 with FPG replacing HbA1c in the model without imputation. The observed FPG and change from Baseline FPG will be summarized descriptively and presented graphically. The least squares means (and standard errors) of change from Baseline FPG will be plotted by treatment group. The analyses will be performed on ITT population and all data will be listed.

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

HbA_{1c} change from baseline by visit will be analyzed using the same MMRM model as described in Section 7.1.1.1 without imputation in the ITT 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.

8.2. Safety and Tolerability Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the safety population.

Safety and exposure for subjects continuing in extension study 204682 will be summarized too.

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

Table 5 Overview of Planned Safety Analyses

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Injection Site Reaction	Y			Y				
Immunogenicity	Y			Y				
Adverse Events								
All AEs	Y			Y				
Pre-therapy, On-therapy, and Post-therapy 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				
Incidence of hypoglycemic events (in total and by each category as defined by the American Diabetes Association criteria)	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.

8.2.2. Injection Site Reactions

Injection site reactions are reported by the investigators on the eCRF. The number and percentage of subjects with injection site reactions and 95% confidence intervals of the proportions will be presented by treatment group. In addition, the time to first occurrence of an injection site reaction will be analyzed and presented in a manner identical to that described for the first occurrence of a GI event in Section 8.2.7.5.

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.

8.2.3. Immunogenicity

Serum for antidrug antibody testing will be obtained from all subjects before administration of study treatment at Week 0, 2, 4, 8, 12, 16, 20, 24, 26/early withdrawal and at follow-up (if applicable), according to the Time and Events Table in Appendix 2. The presence of anti-albiglutide antibodies will be assessed using a validated enzymelinked immunosorbent assay. The assay involves screening, confirmation, and titration steps (tiered-testing approach). Confirmed positive samples will be titrated to obtain the titre of antibodies and tested for GLP-1 and albumin cross-reactivity, as well as for albiglutide neutralizing activity. Samples positive for both anti-GLP-1 antibodies and drug neutralizing antibodies may be tested for GLP-1 neutralizing activity.

Anti-albiglutide antibody results will be analyzed by treatment arm, visit, and study period for the safety population. For subjects with positive anti-albiglutide antibody results, the number and percentage with positive albiglutide neutralizing antibody results, positive anti-GLP-1 antibody results, and positive anti-albumin antibody results will be provided separately at each assessment. The 95% confidence intervals for the proportions of the positive immunogenicity results will be calculated using exact binomial method, assuming a simple binomial distribution. Antibody titers will be summarized using descriptive statistics. Individual immunogenicity data, including antibody titers, will be listed for each subject.

Additionally, in the case of severe allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions, three 1-mL serum samples should be obtained for immunogenicity testing (within 24 hours of the event if possible) and sent to the central laboratory for immediate distribution to a contracted testing facility for specific immunological testing (albiglutide specific IgE and other tests,

as appropriate) A follow-up serum sample will be collected 8 weeks after the final dose of study treatment in the case of early withdrawal from the study. For subjects who have discontinued study treatment or subjects who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682), if baseline antibody levels or a reduction in titer are not achieved by the follow-up visit then additional samples for immunogenicity testing may be obtained every 30 days following the follow-up visit until baseline antibody levels, or reduced titres, are achieved. Subjects eligible for the extension study (Study 204682) will have immunogenicity samples taken as specified in protocol 204682.

The immunogenicity data in the case of severe allergic reactions will be listed.

8.2.4. 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, will be provided. Adverse events will also be summarized by maximum intensity (mild, moderate, and severe).

AE summaries will not include hypoglycemic events, unless otherwise specified – The exceptions are summaries for serious AEs, AEs leading to withdrawal from treatment/study and pre-therapy AEs.

All AEs will be listed in a subject data listing.

8.2.4.1. 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.

8.2.4.2. 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.

8.2.4.3. 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.

8.2.4.4. 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).

8.2.4.5. 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.

8.2.5. 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.

8.2.6. 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 study treatment from the study will be presented by treatment group for the on-therapy phase.

A summary of the number and percentage of subjects with adverse events leading to withdrawal from the study will be presented 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.

8.2.7. 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, summary tables and by subject data listings will be provided.

8.2.7.1. 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.

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.

8.2.7.2. 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.

8.2.7.3. 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.

8.2.7.4. 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.

8.2.7.5. 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 + 25 days. 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.

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.

8.2.7.6. 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.

8.2.7.7. 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.

8.2.7.8. 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.

8.2.7.9. 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 customized MedDRA query 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.

8.2.7.10. 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.

8.2.7.11. 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.

8.2.7.12. 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.

8.2.8. Pregnancies

A listing of subject pregnancies will be provided.

8.2.9. Clinical Laboratory Evaluations

Laboratory results that are beyond the limits of quantification will have the inequality sign dropped ($<$, $\leq$, $>$, or $\geq$) and the quantification limit will be used as the numeric result for summarization.

8.2.9.1. 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 central lab for the study records.

Hematology parameters used in summaries include complete blood count with red blood cell indices, white blood cell count with differential, and platelet count. Chemistry parameters (including lipids) used in summaries include blood urea nitrogen (BUN),

potassium, aspartate aminotransferase (AST), total and direct bilirubin, creatinine, sodium, ALT, total protein, calcium, chloride, alkaline phosphatase (ALP), albumin, bicarbonate, uric acid, gamma glutamyl transferase (GGT), estimated glomerular filtration rate (eGFR), and lipids (including total cholesterol, LDL-C, HDL C, triglycerides, free fatty acids). Urinalysis include specific gravity, pH, glucose, protein, blood and ketones by dipstick and microscopic examination (if blood or protein is abnormal). Note that white blood cell absolute count was not collected in the study.

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 other laboratory tests, such as HIV, Lipase, Amylase, hepatitis B, hepatitis C, TSH, and urine pregnancy test results.

8.2.10. Other Safety Measures

8.2.10.1. 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.

8.2.10.2. 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.

Additional notable abnormality criteria are defined based on the corrected QT interval (both QTcB and QTcF values) as the following: >450 msec, >480 msec, >500 msec, >30 msc increase from baseline, and >60 msec increase from baseline. The numbers and percentages of subjects who have notable abnormalities at any time post-baseline will be presented overall and by treatment group.

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

8.2.10.3. 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.

8.3. Pharmacokinetic Analyses

Blood samples for the determination of albiglutide plasma concentrations will be obtained from all subjects before administration of study treatment at Week 12 and Week 26/early withdrawal. During visits where ECGs and vital sign measurements are required, blood samples will be collected after measurement of ECGs and vital signs.

Albiglutide concentrations will be summarized by treatment group at each visit using descriptive statistics (n, mean, SD, coefficient of variation [%], median, minimum, maximum, geometric mean and geometric mean coefficient of variation [%]).

Data will be summarized for the PK population and individual subject concentration data will be listed.

8.3.1. Overview of Planned Analyses

The PK analyses will be based on the PK 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 PK Analyses

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Summary of [Analyte] [Matrix] Pharmacokinetic Concentration-Time Data by treatment group	Y		Y	Y				
Summary of [Analyte] Pharmacokinetic Urine Excretion Rate-Time Data by treatment group	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.

8.4. 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.

9. OTHER STATISTICAL ANALYSES

Not applicable.

10. REFERENCES

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11. APPENDICES

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

11.1.1. Exclusions from Per Protocol Population

Final list of protocol deviations that lead to exclusion from Per-Protocol population will be determined by the study team and populated here toward the end of the study.

A subject meeting any of the following criteria may be excluded from the Per Protocol population based on clinical judgement in a case-by-case basis. In addition, other deviations that may not fall under the following criteria may be excluded from the per protocol population based on a case by case basis:

Number	Protocol Deviation Description
01	Concomitant Medication • Subject took medication prohibited by protocol (SAFETY) • Subject took medication prohibited by protocol (EFFICACY)
02	Study Treatment Compliance • Subject did not receive >= 80% of planned medication
03	Inclusion Criteria and Exclusion Criteria • Subject enrolled but did not meet all protocol inclusion criteria at screening. • Subject enrolled but met exclusion criteria at screening.
04	Study Treatment Admin/Dispense • Incorrect study medication kit and/or pen dispensed to subject.
05	ICF (Informed Consent Form) Process/Timing • ICF(s) not obtained prior to any study procedure. • Site staff did not sign and/or date ICF. • Genetic blood sample collected without subject consent. • ICF re-consenting issues/delays • Incorrect ICF used
06	Missing Endpoint Assessments • HbA1c blood sample not collected or insufficient/deficient at baseline or Week 26

11.1.2. Significant Protocol Deviation Rules

The Significant Protocol Deviation Rules Version 1.1, dated 21JUN2017, 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.

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

Procedure		Treatment													
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Week[15]	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
	Visit Window	**-14d**	**0d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**
Informed consent		X													
Demography/medical history		X													
HIV, hepatitis B and C, amylase, lipase, alcohol and drug screen, TSH		X													
Inclusion/exclusion criteria review		X	X[1]												
Full (F) or brief (B) physical exam[2]		F	B				B				B				
Height (H),Weigh (W), BMI		H, W, BMI					W				W				
12-lead ECG[3]		X	X		X		X				X				
Vital signs[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum (S)/Urine (U) pregnancy test (WCBP)		S	U	U			U				U				
Clinical chemistry/hematology samples[4]		X		X			X				X				
Lipids (including total cholesterol, LDL-C, HDL C, triglycerides, FFAs)[4]		X													
Urinalysis		X													
HbA_{1c} [5, 8]		X	X	X			X				X				X
eGFR		X		X							X				
Immunogenicity sample[6]			X		X		X				X				X
Genetic sample[7]			X												
FPG [8]			X	X	X	X	X	X	X	X	X	X	X	X	X
PK samples[9]															X
Review AE/SAE, concomitant medication and hypoglycemia events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Advice on diet and exercise[10]			X	X	X	X	X	X	X	X	X	X	X	X	X
Register visit into IVRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Randomization[11]		X												
Study Treatment		X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure		**Treatment**													**End of Treatment** [12, 13]	**Follow-up**[14]
	Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
	Week[15]	***13***	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**34**
	Visit Window	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**
Informed consent																
Demography/medical history																
HIV, hepatitis B and C, amylase, lipase, alcohol and drug screen, TSH																
Inclusion/exclusion criteria review																
Full (F) or brief (B) physical exam[2]		B			B				B					B	F	F
Height (H),Weigh (W), BMI		W			W				W					W	W	W
12-lead ECG[3]															X	
Vital signs			X		X		X		X		X			X	X	X
Serum (S)/Urine (U) pregnancy test (WCBP)		U			U				U					U	S	U
Clinical chemistry/hematology samples[4]					X										X	
Lipids (including total cholesterol, LDL-C, HDL C, triglycerides, FFAs)[4]															X	X
Urinalysis															X	
HbA_{1c} [5, 8]					X				X						X	X
eGFR					X										X	X
Immunogenicity sample[6]					X				X				X		X	X
Genetic sample[7]																
FPG [8]		X			X				X						X	X
PK samples[9]															X	
Review AE/SAE, concomitant medication and hypoglycemia events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Advice on diet and exercise[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Register visit into IVRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[11]																

Procedure		Treatment													End of Treatment [12, 13]	Follow-up[14]
	Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
	Week[15]	***13***	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**34**
	Visit Window	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**
Study Treatment		X	X	X	X	X	X	X	X	X	X	X	X	X		

TSH: thyroid stimulating hormone; BMI: body mass index; WCBP: women of child bearing potential; FFA: free fatty acids; LDL-c: low density lipoproteins cholesterol; HDL-c: high density lipoproteins cholesterol; d, day

1. **Before dosing**, the investigator must review **all** inclusion and exclusion criteria to confirm subject's eligibility. If a subject no longer meets all of the eligibility criteria (e.g., there is evidence of a new myocardial infarction (MI) on an ECG or ALT, etc. are out of range), **do not administer the study treatment** and contact the medical monitor to discuss how to proceed (e.g., to determine if repeat testing is warranted).
2. Details of full and brief physical examinations are provided in Protocol Section 7.4.3.
3. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. Vital signs measurement will be taken before collection of blood samples. See Protocol Section 7.4.5.
4. Clinical chemistry and hematology assessments are described in Protocol Section 7.4.6.
5. Blood samples for HbA_{1c} should be collected before administration of study treatment.
6. Blood samples for immunogenicity are to be collected **before** study drug administration at the times specified in Protocol Section 7.1. A follow-up sample will be taken from each subject 8 weeks after the final dose of albiglutide is administered.
7. Blood sample for genetics 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.
8. Subjects will have their FPG and HbA_{1c} levels evaluated to monitor for potential hyperglycemia.
9. PK samples (trough) will be obtained prior to dosing (Protocol Section 7.6).
10. Standard diabetic dietary and exercise advice will be provided at Visit 2 and reinforced through the end-of-treatment visit.
11. Once the HbA_{1c} results have been received from the central laboratory and all other eligibility criteria are met, study centre personnel will call the IVRS to obtain the subject's treatment assignment.
12. Subjects who discontinue study treatment should be handled as described in Protocol Section 5.5.
13. The end of treatment visit in Study 200952.is also Visit 1 of 204682 for those subjects continuing into the extension study.
14. Follow-up visit for subjects who have stopped investigational product (see Protocol Section 5.5), withdrawn from the study or who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).
15. All visits will have a treatment window as in the table. Baseline (Week 0) serves as the reference point. Subjects will not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit within the above window (e.g., holidays, vacations, personal emergencies). Determination of the maximum visit window deviation is at the discretion of the medical monitor

11.2.2. Schedule of Assessments for Subjects Who Permanently Discontinue Investigational Product

Procedure	Continue Scheduled Clinic Visit (Weeks 4, 8, 12,16,20) [4,5]	Week 26 (Equivalent to End of Treatment Visit)	Follow-up Week 34
Full (F) or brief (B) physical exam	B	F	F
Weight	X	X	X
12-lead ECG [1]		X	X
Vital Signs	X	X	X
Clinical chemistry/hematology samples[2]	X	X	X
HbA1c and FPG [3]	X	X	X
Review AE/SAE, concomitant medication and hypoglycaemia events	X	X	X

1. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. Vital signs measurement will be taken before collection of blood sample. See Protocol Section 7.4.5.
2. Clinical chemistry and hematology assessments are described in Protocol Section 7.4.6.
3. Subjects will have their FPG and HbA1c levels evaluated to monitor for potential hyperglycemia.
4. Week will be dependent on when the subject discontinues investigational product. Subjects will start this schedule as soon as possible following investigational product discontinuation and timings of visits will be the same as for if the subject was continuing on investigational product. The timing of the clinic visits can be modified at the discretion of the investigator. All subjects must attend the Week 26 visit.
5. Additional unscheduled visits will occur as medically necessary.

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of 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.

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 respective Table Analysis Visit Windows below to slot the record to the appropriate analysis visit.

   Safety assessments:

   - For records determined to be in the pre-therapy period, the Screening (Week -2) and Baseline (Week 0) analysis visits will be based on the nominal visits recorded on the eCRF.
   - For records determined to be in the on-therapy period, use the study day with the slotting intervals in the respective 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 34 post-therapy analysis visit. For subjects who terminate study treatment early, all post-therapy period records will be assigned to the 8 Week Follow up Visit.

Efficacy assessments (HbA1c and FPG):

- For records determined to be in the pre-therapy period, the Screening (Week -2) and Baseline (Week 0) analysis visits will be based on the nominal visits recorded on the eCRF.
- For records determined to be in the on-therapy or post-therapy period, use the study day with the slotting intervals in the respective table below to assign the records to the appropriate on-therapy analysis visit (Week 1 through Week 34).

11.3.3. 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 post-baseline assessments; for baseline, it is the record latest in time

11.3.4. Analysis Visit Windows

For vital sign assessments (except weight):

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Screening (Week -2)	-14	Not applicable
Baseline (Week 0)	1	Not applicable
On-therapy		
Week 1	8	2 to 11 days
Week 2	15	12 to 18 days
Week 3	22	19 to 25 days
Week 4	29	26 to 32 days
Week 5	36	33 to 39 days
Week 6	43	40 to 46 days
Week 7	50	47 to 53 days
Week 8	57	54 to 60 days
Week 9	64	61 to 67 days
Week 10	71	68 to 74 days
Week 11	78	75 to 81 days
Week 12	85	82 to 92 days
Week 14	99	93 to 106 days
Week 16	113	107 to 120 days
Week 18	127	121 to 134 days

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Week 20	141	135 to 148 days
Week 22	155	149 to 165 days
Week 25	176	166 to 179 days
Week 26 (End of Treatment Visit)*	183	180 to (last dose date + 25 days)
Post-therapy		
Week 34**	239	>Last dose date + 25 days
8 Week Follow-up Visit**	Last dose date + 63 days***	>Last dose date + 25 days

* Week 26 is the end of treatment visit for those subjects completing the study per-protocol. For subjects who withdraw early from study 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 34 is the 8 week post-treatment follow-up visit for those subjects completing the study per-protocol. The 8 Week Follow-up Visit is the 8 week post-treatment follow-up visit for those subjects who withdraw early from study treatment. Both visits will be assigned based on the visit slotting algorithm using therapy phase.
*** The target study day for the 8 Week Follow-up Visit for subjects who withdraw early from study treatment is set to be 9 weeks (63 days) after last dose to correspond with the timing of the 8 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 34).

For ECG assessments:

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Week -2	-14	Not applicable
Baseline (Week 0)	1	Not applicable
On-therapy		
Week 2	15	2 to 22 days
Week 4	29	23 to 43 days
Week 8	57	44 to 120 days
Week 26 (End of Treatment Visit)*	183	121 to (last dose date + 25 days)
Post-therapy		
Week 34**	239	>Last dose date + 25 days
8 Week Follow-up Visit**	Last dose date + 63 days***	>Last dose date + 25 days

* Week 26 is the end of treatment visit for those subjects completing the study per-protocol. For subjects who withdraw early from study 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 34 is the 8 week post-treatment follow-up visit for those subjects completing the study per-protocol. The 8 Week Follow-up Visit is the 8 week post-treatment follow-up visit for those subjects who withdraw early from study treatment. Both visits will be assigned based on the visit slotting algorithm using therapy phase.
*** The target study day for the 8 Week Follow-up Visit for subjects who withdraw early from study treatment is set to be 9 weeks (63 days) after last dose to correspond with the timing of the 8 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 34).

For lab assessments:

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Week -2	-14	Not applicable
On-therapy		
Week 1	8	2 to 18 days
Week 4	29	19 to 43 days
Week 8	57	44 to 85 days
Week 16	113	86 to 148 days

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Week 26 (End of Treatment Visit)*	183	149 to (last dose date + 25 days)
Post-therapy		
Week 34**	239	>Last dose date + 25 days
8 Week Follow-up Visit**	Last dose date + 63 days***	>Last dose date + 25 days
* Week 26 is the end of treatment visit for those subjects completing the study per-protocol. For subjects who withdraw early from study 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 34 is the 8 week post-treatment follow-up visit for those subjects completing the study per-protocol. The 8 Week Follow-up Visit is the 8 week post-treatment follow-up visit for those subjects who withdraw early from study treatment. Both visits will be assigned based on the visit slotting algorithm using therapy phase. *** The target study day for the 8 Week Follow-up Visit for subjects who withdraw early from study treatment is set to be 9 weeks (63 days) after last dose to correspond with the timing of the 8 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 34).		

For immunogenicity assessments:

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Baseline (Week 0)	1	Not applicable
On-therapy		
Week 2	15	2 to 22 days
Week 4	29	23 to 43 days
Week 8	57	44 to 71 days
Week 12	85	72 to 99 days
Week 16	113	100 to 127 days
Week 20	141	128 to 155 days
Week 24	169	156 to 176 days
Week 26 (End of Treatment Visit)*	183	177 to (last dose date + 25 days)
Post-therapy		
Week 34**	239	>Last dose date + 25 days
8 Week Follow-up Visit**	Last dose date + 63 days***	>Last dose date + 25 days
* Week 26 is the end of treatment visit for those subjects completing the study per-protocol. For subjects who withdraw early from study 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 34 is the 8 week post-treatment follow-up visit for those subjects completing the study per-protocol. The 8 Week Follow-up Visit is the 8 week post-treatment follow-up visit for those subjects who withdraw early from study treatment. Both visits will be assigned based on the visit slotting algorithm using therapy phase. *** The target study day for the 8 Week Follow-up Visit for subjects who withdraw early from study treatment is set to be 9 weeks (63 days) after last dose to correspond with the timing of the 8 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 34).		

For weight assessments:

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Week -2	-14	Not applicable
On-therapy		

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Week 4	29	2 to 43 days
Week 8	57	44 to 74 days
Week 13	92	75 to 102 days
Week 16	113	103 to 127 days
Week 20	141	128 to 158 days
Week 25	176	159 to 179 days
Week 26 (End of Treatment Visit)*	183	180 to (last dose date + 25 days)
Post-therapy		
Week 34**	239	>Last dose date + 25 days
8 Week Follow-up Visit**	Last dose date + 63 days***	>Last dose date + 25 days
* Week 26 is the end of treatment visit for those subjects completing the study per-protocol. For subjects who withdraw early from study 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 34 is the 8 week post-treatment follow-up visit for those subjects completing the study per-protocol. The 8 Week Follow-up Visit is the 8 week post-treatment follow-up visit for those subjects who withdraw early from study treatment. Both visits will be assigned based on the visit slotting algorithm using therapy phase. *** The target study day for the 8 Week Follow-up Visit for subjects who withdraw early from study treatment is set to be 9 weeks (63 days) after last dose to correspond with the timing of the 8 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 34).		

For HbA1C assessments:

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Week -2	-14	Not applicable
Baseline (Week 0)	1	Not applicable
On-therapy or post-therapy*		
Week 1	8	2 to 18 days
Week 4	29	19 to 43 days
Week 8	57	44 to 71 days
Week 12	85	72 to 99 days
Week 16	113	100 to 127 days
Week 20	141	128 to 162 days
Week 26 (End of Treatment Visit)	183	163 to 211 days
Week 34	239	>211 days
* For all subjects regardless their study drug discontinuation status, their on-therapy or post-therapy period assessments will be slotted in the same way to the appropriate analysis visits per the above defined slotting intervals.		

For FPG assessments:

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Pre-therapy		
Baseline (Week 0)	1	Not applicable
On-therapy or post-therapy*		
Week 1	8	2 to 11 days
Week 2	15	12 to 18 days
Week 3	22	19 to 25 days
Week 4	29	26 to 32 days
Week 5	36	33 tp 39 days

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Week 6	43	40 to 46 days
Week 7	50	47 to 53 days
Week 8	57	54 to 60 days
Week 9	64	61 to 67 days
Week 10	71	68 to 74 days
Week 11	78	75 to 81 days
Week 12	85	82 to 88 days
Week 13	92	89 to 102 days
Week 16	113	103 to 127 days
Week 20	141	128 to 162 days
Week 26 (End of Treatment Visit)	183	163 to 211 days
Week 34	239	>211 days
* For all subjects regardless their study drug discontinuation status, their on-therapy or post-therapy period assessments will be slotted in the same way to the appropriate analysis visits per the above defined slotting intervals.		

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 25 days after the date of last dose.
- **Post-therapy:** The onset date of the AE is more than 25 days after the last date of randomized study medication.

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 25 days after the date of last dose.
- **Post-therapy:** The assessment date is more than 25 days after the last date of randomized study medication.

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, then the imputed start date will always be on or prior to the stop date.

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 nonmissing 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) and then 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 in the eCRF. Subjects who discontinue active participation in the study will no longer receive the randomized study treatment. Immediately upon discontinuation from active participation in this study, these subjects should complete the early withdrawal assessments and return 8 weeks later for the follow-up assessments.

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

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. Handling of Missing Data

11.6.3.1. Impact of Missing Data on Primary Endpoint

Missing data, in the context of the primary analysis at Week 26, refer to those cases where the Week 26 HbA1c value is not available or was not collected or subject is lost to follow-up or withdraws consent. Missing data will be imputed in the primary MMRM analysis. To avoid bias in non-inferiority trials due to missing data, special attention will be paid to the handling of missing data in statistical analysis. Although, it is expected that the pattern of missing data will be similar in both treatment arms given that the treatment arms are the same drug but different formulations and it is expected that the impact of missing data on the primary endpoint to be minimal. Imputation under the non-inferiority null hypothesis [Koch, 2008] for all missing data for the primary analysis at Week 26 will be implemented.

11.6.3.2. Extent of Missing Primary Analysis Data

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 HbA1c between two non-missing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment will stay in the study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA1c 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 lost to follow-up or withdrawal of consent or investigator discretion.

11.6.3.3. Reasons for Withdrawal

Reasons for withdrawal from the study are lost to follow-up or withdrawal consent or investigator discretion. All subjects who discontinuation from investigational product due to the reason listed under protocol Section 5.5 will remain in the study and efficacy and safety data will be collected.

11.6.3.4. Sensitivity Analysis Under Missing Not At Random (MNAR)

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

Examination of Missing Data Patterns

It is expected that the pattern of missing data will be similar in both treatment groups given the each treatment group is using the same drug but different formula.

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA1c change from baseline) that were completed at Weeks 1, 4, 8, 12, 16, 20, and 26.

- Subjects who have week 1 assessment only
- Subjects who have assessments up to and including Week 4 only
- Subjects who have assessments up to and including Week 8 only
- Subjects who have assessments up to and including Week 12 only
- Subjects who have assessments up to and including Week 16 only
- Subjects who have assessments up to and including Week 20 only
- Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 7 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

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.

To assess the impact of subjects who discontinued investigational product and stayed in the study; exclusion of data after treatment discontinuation may also be performed if a significant number of subjects discontinue study medication prior to Week 26. On treatment data will be analyzed using the same imputation/MMRM model as described in Section 7.1.1.1. The imputation will be performed for missing value at Week 26 due to any reason and also available value at Week 26, but off-treatment.

Sensitivity analyses using a different type of multiple imputation method will be conducted. Firstly, missing data between two non-missing time points (i.e. intermittent missing data) will be considered missing at random (MAR). Secondly, missing data after the last available assessment due to any reasons (i.e. monotone missing data) will be imputed using last mean carried forward (LMCF), that is Missing Not At Random (MNAR) (Carpenter and Kenward, 2013). Thirdly, this approach assumes that a constant rate of increase in HbA_{1c} change from Baseline is experienced by subjects following withdrawal from the study. The imputed values based on LMCF will be then updated with an added delta using the following rates of HbA1c 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 HbA1c increase. This estimand is one where those who withdraw are assumed to revert to an unstable treatment regimen with an increasing rate of HbA1c. For each imputation data set, an analysis of variance (ANCOVA) 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 this multiple imputation approach using delta method in combination with LMCF are the following:

- Step 1: Multiple Imputation under MAR (***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 (**μ**) and variance-covariance matrices (∑) 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 $\sum_{22} - \sum_{21} \sum_{11}^{-1} \sum_{12}$. So, 100 imputed datasets are generated.
- Step 2: Multiple Imputation using LMCF (K=100 times)
  - For each imputed dataset from Step 1, update the imputed values (post-last observation) as follows:
    - For each subject per treatment group, if there are any imputed values after the last observation (Yp, imp), first split the simulated mean vector (μ) into three parts: μb (prior to last obs), μlast (last obs) and μp (post last obs) and then update these imputed values as Y*p, imp=(Yp, imp - μp + μlast). Repeat for all subjects and for both treatment groups.
  - Repeat for the 100 imputed datasets from Step 1.
- Step 3: Multiple Imputation using Delta method (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 liquid and lyophilized 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 liquid treatment group, the delta value = $\gamma_1 \times \tau/4$; if the subject belongs to the lyophilized 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: Repeat Step 1, Step 2 and Step 3 for 9 scenarios based on 3 different rates of HbA1c increase for each treatment group (i.e. γ_1, γ_2=0/month , 0.1/month and 0.2/month)
- Step 5: For each scenario, apply ANCOVA analysis at Week 26 for each of the 100 imputed dataset and save the difference in LSmeans between treatment group and the associated standard error from each of the 100 analyses.
- Step 6: For each scenario, 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.

11.6.3.5. Sensitivity Analysis for Potential Data Fabrication

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

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

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Calcium	mmol/L	None	<1.8 mmol/L >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
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

Liver Function Tests

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

11.8.1. Definition of 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 clustering will be finalized after clinical site selection and randomization are complete.

- Final classification of geographic region

Region	State	Investigational Site
USA - North	New York, Pennsylvania, Ohio, Indiana, Illinois, Michigan, Missouri, Nebraska, Kansas	PPD
USA – South Atlantic	North Carolina, South Carolina, Georgia, Florida	
USA – South Central	Kentucky, Alabama, Arkansas, Louisiana, Texas	
USA - West	Idaho, Colorado, New Mexico, Arizona, Utah, Nevada, Washington, California	

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:

- Age at randomization (<65 years versus ≥65 years)
- Weight at Screening (<90 or >=90 kg)
- Background antidiabetic therapy (diet and exercise or stable dose of metformin)

The primary analysis of HbA1c change from baseline will use a mixed-effect model with repeated measures (MMRM), which includes HbA1c change from baseline at all post-baseline visits as dependent variables; treatment, region, age category, weight category, backgroup antidiabetic therapy, visit week, treatment-by-visit interaction as fixed effects; baseline HbA_{1c} as a continuous covariate; and subject as a random effect.

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 HbA1c (< 8% or >=8%)
- Region (USA – North, USA – South Atlantic, USA – South Central, USA - West)
- Age at randomization (<65 or >=65 years)
- Weight at Screening (<90 or >=90 kg)
- Background antidiabetic therapy (diet and exercise or stable dose of metformin)
- Gender (male or female)
- Race (white or non-white)
- Ethnicity (Hispanic or non-hispanic)
- Duration of diabetes category (<5, 5 to 10 or >10 years)

11.10. Appendix 10: Multiple Comparisons & Multiplicity

11.10.1. Handling of Multiple Comparisons & Multiplicity

Not applicable.

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 with imputation

Step 1a: Transpose the data horizontally and then impute data assuming missing at random (EFFIM)

```
PROC MI DATA= EFF OUT= EFFIM NIMPUTE=100 SEED=4408572;
   BY TRT01PN;
   MCMC CHAIN=multiple;
   VAR BASE CHG_W1 CHG_W4 CHG_W8 CHG_W12 CHG_W16 CHG_W20 CHG_W26;
   RUN;
```

Note: need to remove all imputed values before Week 26 and retain imputed values at Week 26 only.

Step 1b: Add 0.4 to the imputed value at Week 26 in the liquid product arm and transpose data in vertical structure (EFFIM2)

Step 2: Exclude HbA1c change from baseline at Week 1 and perform MMRM for each imputed dataset

```
Ods output SLICES=SLICELSM SLICEDIFFS=SLICEDIFF;

PROC MIXED DATA= EFFIM ;
   BY _imputation_;
   CLASS USUBJID REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN;
   MODEL CHG= BASE REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN
TRT01PN*AVISITN BASE*AVISITN/ DDFM=KR;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   SLICE TRT01PN*AVISITN/sliceby(AVISITN='26') means pdiff cl cov;
RUN;
```

Step 3: Combine results using PROC MIANALYZE

```
PROC SORT DATA=SLICELSM; BY TRT01PN IMPUTATION; RUN;
PROC MIANALYZE DATA=SLICELSM EDF=CDF*;
BY TRT01PN;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
RUN;

PROC MIANALYZE DATA=SLICEDIFF;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
RUN;

*CDF=complete-data degrees of freedom. This is used to calculate the
adjusted degrees of freedom for the combined results.
```

2. Example SAS code for the by-subgroup analysis of the primary endpoint with imputation

Follow the same steps as for the example SAS code for the primary analysis except in the step 2 additional interaction terms need to be added.

```
Subgroup variable: Baseline HbA1c <8% or >=8%
ods output SLICES=SLICELSM1 SLICEDIFFS=SLICEDIFF1;
PROC MIXED DATA= EFFIM;
   BY imputation;
   CLASS USUBJID REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN HBGR1;
   MODEL CHG= HBGR1 REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN
TRT01PN*AVISITN HBGR1*TRT01PN HBGR1*AVISITN
             HBGR1*TRT01PN*AVISITN/ DDFM=KR;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   SLICE HBGR1*TRT01PN*AVISITN/sliceby(AVISITN='26') means pdiff cl
cov;
RUN;

Subgroup variable: Baseline Weight <90 or >=90 kg
ods output SLICES=SLICELSM2 SLICEDIFFS=SLICEDIFF2;
PROC MIXED DATA= EFFIM;
   BY imputation;
   CLASS USUBJID REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN;
   MODEL CHG= BASE REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN
TRT01PN*AVISITN BASE*AVISITN WGTGR1*TRT01PN WGTGR1*AVISITN
             WGTGR1*TRT01PN*AVISITN/ DDFM=KR;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   SLICE WGTGR1*TRT01PN*AVISITN/sliceby(AVISITN='26') means pdiff cl
cov;
RUN;
```

3. Example SAS code for the secondary efficacy analyses using MMRM without imputation

```
PROC MIXED DATA= INDATA ;
   CLASS USUBJID REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN;
   MODEL CHG= BASE REGION WGTGR1 AGEGR1 PRIORDTX TRT01PN AVISITN
TRT01PN*AVISITN BASE*AVISITN/ DDFM=KR;
   REPEATED AVISITN/SUB=USUBJID TYPE=UN;
   SLICE TRT01PN*AVISITN/slice=AVISITN means pdiff cl cov;
RUN;
```

11.12. Appendix 12: Sample Size Considerations

11.12.1. Sample Size Assumptions

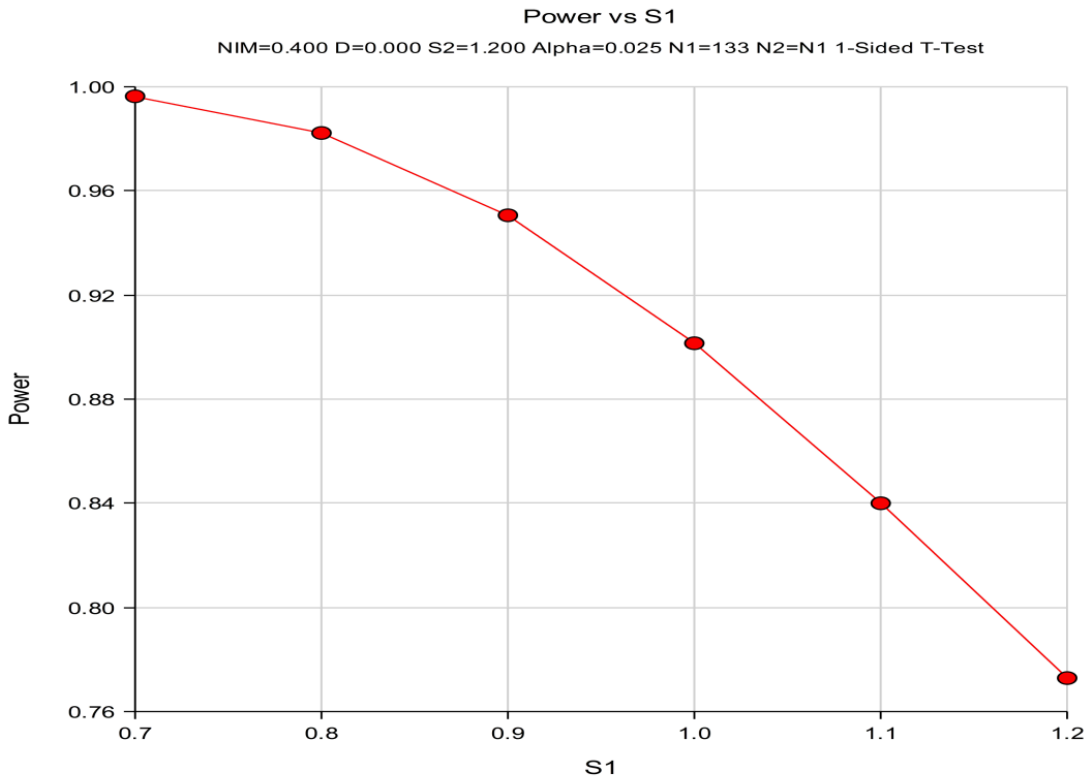
This study will randomly assign approximately 150 subjects to each of the 2 treatment groups (liquid drug product and lyophilized drug product) in a 1:1 ratio, for a total of approximately 300 subjects. Eligible subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin).

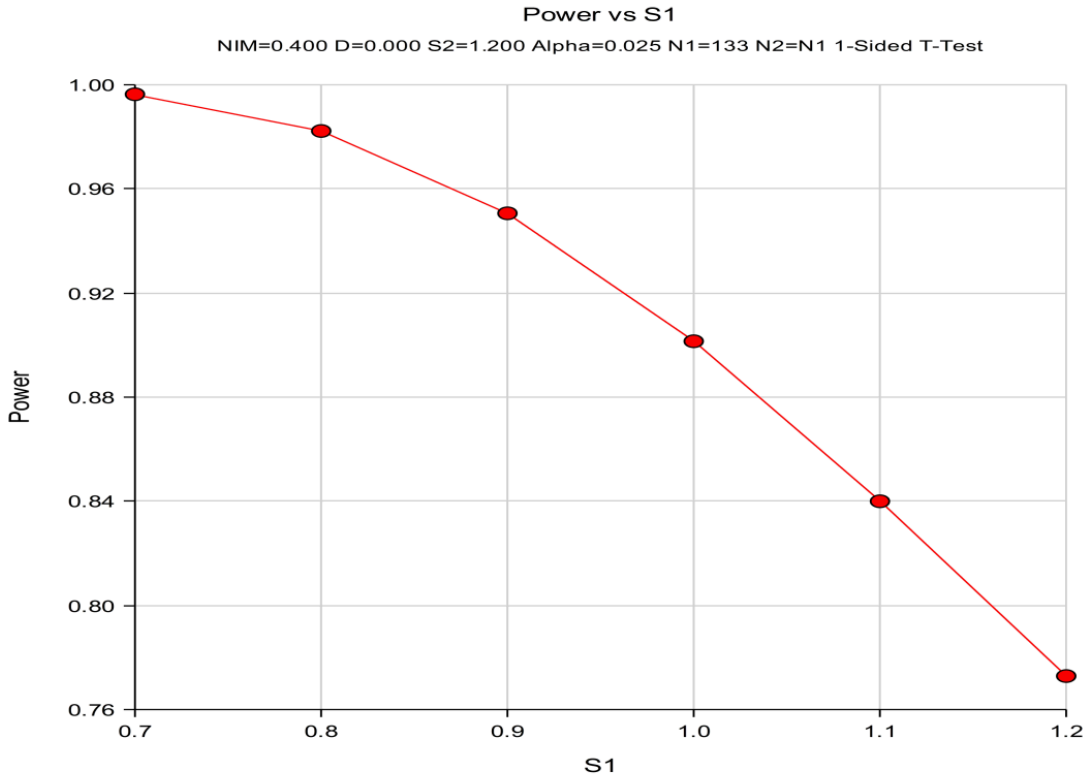
With 133 subjects in each of the 2 treatment groups, the study will provide 90% power to demonstrate non-inferiority for HbA1c change from baseline, assuming a non-inferiority margin of 0.4%, an expected treatment group difference of 0.0%, and a common standard deviation of 1%, using a 2-sample, 1-sided t test with significance level of 0.025. Power was calculated using PASS [Hintze, 2013]. Assuming that 13% of subjects will be withdrawn early or will be lost to follow-up; therefore, approximately 150 subjects will be randomized in each treatment group.

The non-inferiority margin of 0.40 was selected based on the expected effect of the albiglutide lyophilized drug product as active control. Results from two HARMONY Phase III studies (subset of GLP112756 and GLP112753) for the comparison of the control albiglutide lyophilized drug product versus placebo were used in selecting the non-inferiority margin. The two studies are similar to the current study in terms of the population and the design; subjects were either on diet and exercise or metformin background therapy and received 30 mg of albiglutide then up-titrated to 50 mg albiglutide. The 95% confidence interval from the 2 Harmony studies for HbA1c change from baseline at week 24 for albiglutide lyophilized drug product difference from placebo is (-1.04, -0.75). The conservative effect in terms of the difference from placebo for HbA1c change from baseline at Week 24 for albiglutide lyophilized drug product versus placebo is 0.75% (M1 =0.75%, as defined in Guidance for Industry: Non-Inferiority Clinical Trials [FDA, 2010]). M2, calculated as 50% of M1 is 0.375 (approximately 0.4).The margin of 0.40% that should be met in this trial will preserve at least 45% of the effect of the comparator and it is below M1.

11.12.2. Sample Size Sensitivity

The following Figure illustrates the power versus standard deviation of 0.7, 0.8, 0.9, 1.0, 1.1, and 1.2 to reject the null hypothesis of inferiority for HbA1c change from baseline, assuming a non-inferiority margin of 0.4%, an expected treatment group difference of 0.0%, and a sample size of 133 per treatment group, using a 2-sample, 1-sided t- test with a significance level of 0.025.


Power vs S1
NIM=0.400 D=0.000 S2=1.200 Alpha=0.025 N1=133 N2=N1 1-Sided T-Test
Power
1.00
0.96
0.92
0.88
0.84
0.80
0.76
0.7
0.8
0.9
1.0
1.1
1.2
S1


Power vs S1
NIM=0.400 D=0.000 S2=1.200 Alpha=0.025 N1=133 N2=N1 1-Sided T-Test
Power
1.00
0.96
0.92
0.88
0.84
0.80
0.76
0.7
0.8
0.9
1.0
1.1
1.2
S1

11.12.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned for this study.

11.13. Appendix 13 – Abbreviations & Trade Marks

Abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CV	cardiovascular
DCC	dual chamber cartridge
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FFA	free fatty acids
FPG	fasting plasma glucose
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HA	human albumin
HbA1c	glycated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
hCG	human chorionic gonadotrophin
HDL-c	high density lipoproteins
HRP	horseradish peroxidase
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
INR	international normal range
IP	investigational product
IRB	Institutional Review Board
ISRs	injection site reactions
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LDL-c	low density lipoproteins;
LMCF	last mean carried forward
K_2EDTA	di-potassium ethylenediaminetetraacetic acid
MACE	major adverse cardiovascular event
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
OC RDC	Oracle Clinical Remote Data Capture
PAC	Pancreatitis Adjudication Committee
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PTS-DPMK	Platform Technologies and Science-Drug Metabolism and Pharmacokinetics
RAP	Reporting Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
s.c.	subcutaneous
SAC	Statistical Analysis Complete
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SRM	Study Reference Manual
SU	sulfonylureas
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
WBC	white blood cell
WCBP	women of child bearing potential

Trademark Information

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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 1.43	N/A
Efficacy	2.01 to 2.32	2.01 to 2.14
Safety	3.01 to 3.352	3.01 to 3.61
Section	**Listings**	
ICH Listings	1 to 35	
Other Listings	101 to 154	

11.14.2. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition					
1.1.	All Randomized Subjects		Subject Disposition		
1.2.	All Subjects Screened		Reasons for Screening Failures		
1.3.	All Randomized Subjects		Reasons for Withdrawal from Study		
1.4.	All Randomized Subjects		Reasons for Discontinuing Study Treatment		
1.5.	All Randomized Subjects		Subject Status by Visit		
1.6.	All Randomized Subjects		Subjects Randomized across Sites		
1.7.	All Randomized Subjects		Inclusion/Exclusion Criteria Deviations		
Protocol Deviation					

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	All Randomized Subjects		Significant Protocol Deviations		
Demographics and Baseline Characteristics					
1.9.	[Safety]		Demographics and Baseline Characteristics		
1.10.	All Randomized Subjects		Geographic Ancestry		
1.11.	Safety		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 Cancer History		
1.28.	Safety		Current and/or Past Pneumonia Medical History		
1.29.	Safety		Current and/or Past Skin Medical Conditions		
1.30.	Safety		Current and/or Past Thyroid Medical History		
1.31.	Safety		Current and/or Past Other Medical History		
Prior and Concomitant Medications					
1.41.	Safety		Prior Medications		

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.42.	Safety		Concomitant Medications		
1.43.	Safety		Post-therapy Medications		

11.14.3. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
HbA1c					
2.1.	ITT		Primary Analysis - Analysis of Change from Baseline in HbA1c (%) at Week 26 — With Imputation		
2.2.	ITT		Statistical Output Supporting the Primary Analysis of Change from Baseline in HbA1c (%) at Week 26		
2.3.	ITT		Supportive Analysis 1 - Analysis of Change from Baseline in HbA1c (%) at Week 26 — Without Imputation		
2.4.	ITT		Statistical Output Supporting the Supportive Analysis 1 of Change from Baseline in HbA1c (%) at Week 26 — Without Imputation		
2.5.	ITT		Supportive Analysis 2 - Analysis of Change from Baseline in HbA1c (%) at Week 26 — Without Imputation and Excluding Data after Hyperglycemia Rescue and discontinuation from study treatment		
2.6.	ITT		Statistical Output Supporting the Supportive Analysis 2 of Change from Baseline in HbA1c (%) at Week 26 — Without Imputation and Excluding Data after Hyperglycemia Rescue and discontinuation from study treatment		
2.7.	PP		Supportive Analysis 3 — Per Protocol Analysis of Change from Baseline in HbA1c (%) at Week 26 — Without Imputation		
2.8.	PP		Statistical Output Supporting the Supportive Analysis 3 of Per Protocol Analysis of Change from Baseline in HbA1c (%) at Week 26 — Without Imputation		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.9.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Baseline HbA1c Category — With Imputation		
2.10.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Age Category at Randomization — With Imputation		
2.11.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Region — With Imputation		
2.12.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Weight Category at Randomization — With Imputation		
2.13.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Background Antidiabetic Therapy — With Imputation		
2.14.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Gender — With Imputation		
2.15.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Race — With Imputation		
2.16.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Ethnicity — With Imputation		
2.17.	ITT		Subgroup analysis: Analysis of Change from Baseline in HbA1c (%) at Week 26 by Duration of Diabetes Category — With Imputation		
2.18.	ITT		Sensitivity Analysis 1 - Analysis of Change from Baseline in HbA1c (%) at Week 26 — Excluding Data after Treatment Discontinuation and With Imputation		

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	ITT		Sensitivity Analysis 2: Tipping Point Analysis of Change from Baseline in HbA1c (%) at Week 26 — With Imputation		
2.20.	ITT		Examination of the Pattern of Missing HbA1c Values		
2.21.	ITT		Summary Statistics for HbA1c (%) by Visit		
2.22.	ITT		Analysis of Change from Baseline in HbA1c (%) over Time		
FPG					
2.31.	ITT		Summary Statistics for Change from Baseline in Fasting Plasma Glucose (mmol/L) by Visit		
2.32.	ITT		Analysis of Change from Baseline in Fasting Plasma Glucose (mmol/L) by Visit		

11.14.4. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
HbA1c					
2.1.	ITT		Line Graph of Mean (+/- SE) of HbA1c (%) by Treatment Group and Visit		
2.2.	ITT		Line Graph of Mean (+/- SE) of Change from Baseline in HbA1c (%) by Treatment Group and Visit		
2.3.	ITT		Line Graph of LS Mean (+/- SE) of Change from Baseline in HbA1c (%) by Treat Group and Visit — Without Imputation		
2.4.	ITT		Model-adjusted Change from Baseline in HbA1c (%) for Albiglutide liquid vs. Albiglutide lyophilized and 95% CI at Week 26 — With Imputation		
2.5.	ITT		Line Graph of Mean of Change from Baseline in HbA1c (%) by Missing Data Patterns and Treatment		
2.6.	ITT		Model-adjusted Change from Baseline in HbA1c (%) for Albiglutide liquid vs. Albiglutide lyophilized and 95% CI at Week 26 — Supportive Analysis 1 Without Imputation		
2.7.	ITT		Model-adjusted Change from Baseline in HbA1c (%) for Albiglutide liquid vs. Albiglutide lyophilized and 95% CI at Week 26 — Supportive Analysis 2 Without Imputation and Excluding Data after Hyperglycemia Rescue and Discontinuation from Study Treatment		
2.8.	PP		Model-adjusted Change from Baseline in HbA1c (%) for Albiglutide liquid vs. Albiglutide lyophilized and 95% CI at Week 26 — Supportive Analysis 3 of Per Protocol Analysis Without Imputation		

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
FPG					
2.11.	ITT		Line Graph of Mean (+/- SE) of Fasting Plasma Glucose (mmol/L) by Treatment Group and Visit		
2.12.	ITT		Line Graph of Mean (+/- SE) of Change from Baseline in Fasting Plasma Glucose (mmol/L) by Treatment Group and Visit		
2.13.	ITT		Line Graph of LS Mean (+/- SE) of Change from Baseline in Fasting Plasma Glucose (mmol/L) by Treatment Group and Visit — Without Imputation		
2.14.	ITT		Model-adjusted Change from Baseline in Fasting Plasma Glucose (mmol/L) for Albiglutide liquid vs. Albiglutide lyophilized and 95% CI at Week 26 — Without Imputation		

11.14.5. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Compliance					
3.1.	Safety		Exposure to Treatment		
3.2.	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 >2% in Any Treatment Group and the Information on Relation to Treatment		
3.21.	Safety		On-therapy and Post-therapy Adverse Events Related to Study Treatment		
3.22.	Safety		On-therapy Treatment-related Adverse Events		
3.23.	Safety		Post-therapy Treatment-related Adverse Events		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.24.	Safety		On-therapy and Post-therapy Treatment-related Adverse Events		
3.31.	Safety		Overall Summary of 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 Study Treatment		
3.52.	Safety		On-therapy Adverse Events Leading to Withdrawal from Study		
Adverse Events of Special Interest					
3.61.	Safety		Overview of On-therapy Adverse Events of Special Interest		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
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		
3.80.	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		
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 a Gastrointestinal Adverse Event		
3.119.	Safety		On-therapy Nausea over Time		
3.120.	Safety		On-therapy Diarrhea over Time		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
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 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 a Systemic Allergic Reaction Reported by the Investigator		
3.134.	Safety		Kaplan-Meier Analysis of Time to First Occurrence of a 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 an Injection Site Reaction		
3.143.	Safety		On-therapy Injection Site Reaction over Time		
3.144.	Safety		Summary Characteristics of On-therapy Injection Site Reactions		
3.151.	Safety		On-therpy 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		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
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		
Lab Assessments					
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		
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		
[ECG]					
3.341.	Safety		Change from Baseline in ECG Values by Visit		
3.342.	Safety		ECG Values of Clinical Concern by Visit		

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.343.	Safety		Overall ECG Interpretations by Visit		
3.344.	Safety		Shift in ECG Values of Clinical Concern from Baseline to Week 26		
3.345.	Safety		ECG QTcF and QTcB Results of Notable Abnormalities at any time post-baseli		
Immunogenicity					
3.351.	Safety		Positive Immunogenicity Results for Anti-Albiglutide Antibody Positive Subjects by Visit		
3.352.	Safety		Positive Immunogenicity Results for Anti-Albiglutide Antibody Positive Subjects by Therapy Phase		

11.14.6. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events of Special Interest					
3.1.	Safety		On-therapy Hypoglycemic Events over Time		
3.11.	Safety		On-therapy Gastrointestinal Adverse Events Over Time		
3.12.	Safety		On-therapy Nausea Over Time		
3.13.	Safety		On-therapy Diarrhea Over Time		
3.14.	Safety		On-therapy Vomiting Over Time		
3.15.	Safety		On-therapy Nausea or Vomiting Over Time		
3.21.	Safety		On-therapy Injection Site Reaction Over Time		
Lab					
3.31.	Safety		Line Graph of Mean (+/- SE) Results for Hematology Parameters		
3.32.	Safety		Line Graph of Mean (+/- SE) Results for Chemistry Parameters		
3.33.	Safety		Line Graph of Mean (+/- SE) Change from Baseline Results for Hematology Parameters		
3.34.	Safety		Line Graph of Mean (+/- SE) Change from Baseline Results for Chemistry Parameters		
Vital Signs					
3.41.	Safety		Line Graph of Mean (+/- SE) Results for Vital Sign Parameters		
3.42.	Safety		Line Graph of Mean (+/- SE) Change from Baseline Results for Vital Sign Parameters		
ECG					

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.51.	Safety		Line Graph of Mean (+/- SE) Results for ECG Parameters		
3.52.	Safety		Line Graph of Mean (+/- SE) Change from Baseline Results for ECG Parameters		
Immunogenicity					
3.61.	Safety		Number and Percentage of Subjects with Positive Immunogenicity Results for Anti-Albiglutide Antibody Over Time		

11.14.7. ICH Listings

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

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
17.	Safety		Cardiovascular Events - Coronary Revascularization		
18.	Safety		Cardiovascular Events - Peripheral Revascularization		
19.	Safety		Cardiovascular Events - Valvulopathy		
20.	Safety		Pancreatitis Events		
21.	Safety		Thyroid Cancer/Nodules/ Goiter		
22.	Safety		Customized MedDRA Query Identified Thyroid Adverse Events		
23.	Safety		Systemic Allergic Reactions Reported by the Investigator		
24.	Safety		Systemic Allergic Reactions Identified by Customized MedDRA Query		
25.	Safety		Injection Site Reactions		
26.	Safety		Liver Events Identified by a Customized MedDRA Query		
27.	Safety		Atrial Fibrillation/Flutter		
28.	Safety		Pneumonia Reported by the Investigator		
29.	Safety		Pneumonia Reported Identified by a Customized MedDRA Query		
30.	Safety		Diabetic Retinopathy		
31.	Safety		Appendicitis		
32.	Safety		Malignant Neoplasm		
33.	Safety		Hematology Values of Clinical Concern		
34.	Safety		Chemistry Values of Clinical Concern		
35.	Safety		Liver Function Test Results of Clinical Concern		

11.14.8. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
101.	All Randomized Subjects		Randomization Allocation to Treatment		
102.	All Randomized Subjects		Subject Disposition		
103.	All Randomized Subjects		Reasons for Withdrawal from Study		
104.	All Randomized Subjects		Reasons for Discontinuing Study Treatment		
105.	All Subjects Screened		Reasons for Screening Failures		
106.	All Randomized Subjects		Subject Visits		
107.	All Randomized Subjects		Inclusion/Exclusion Criteria Deviations		
108.	All Randomized Subjects		Protocol Deviations		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
110.	All Randomized Subjects		Analysis Populations		
111.	Safety		Demographics and Baseline Characteristics		
112.	All Randomized Subjects		Geographic Ancestry		
113.	Safety		Substance Use		
114.	Safety		Cardiovascular Medical History		
115.	Safety		Diabetes Related Conditions		
116.	Safety		Diabetes Disease History		
117.	Safety		Medical/Surgical Procedure History		
118.	Safety		Gastrointestinal Medical Conditions		
119.	Safety		Cancer History		
120.	Safety		Pneumonia Medical History		
121.	Safety		Skin Medical Conditions		
122.	Safety		Thyroid Medical History		
123.	Safety		Thyroid Cancer History		
124.	Safety		History Benign Thyroid Conditions		
125.	Safety		Thyroid Cancer Family History		
126.	Safety		Pancreatitis Family History		
127.	Safety		Pancreatic Cancer Family History		
128.	Safety		Other Medical History		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
129.	Safety		Hypersensitivity - Past Medical Conditions		
130.	Safety		Prior and Concomitant Medications		
131.	Safety		Albiglutide Administration and Compliance		
132.	All Randomized Subjects		HbA1c (%)		
133.	All Randomized Subjects		Stratifying Factors Used in MMRM Models		
134.	All Randomized Subjects		Subgroup Values Used in Subgroup Analyses		
135.	All Randomized Subjects		Fasting Plasma Glucose (mmol/L)		
136.	Safety		Adverse Events		
138.	Safety		Hematology Laboratory Evaluations		
139.	Safety		Chemistry Laboratory Evaluations		
140.	Safety		Urinalysis Laboratory Evaluations		
142.	Safety		Vital Signs		
143.	Safety		ECG Values		
144.	Safety		Overall ECG Interpretations		
145.	Safety		Pregnancies		
146.	Safety		Liver Events Information		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
147.	Safety		Liver Biopsy		
148.	Safety		Liver Imaging		
149.	Safety		Other Medical/Surgical Procedures		
150.	Safety		Other Lab Results at Screening		
151.	Safety		Immunogenicity Information: Anti-Albiglutide Antibody		
152.	Safety		Listing of Subject Numbers for Individual Adverse events		
153.	Safety		Listing of Relationship between System Organ Class and Verbatim Text		
154.	All Randomized Subjects		Listing of Subjects for Whom the Treatment Blind was Broken During the Study		