NCT Number: NCT02787551

STATISTICAL ANALYSIS PLAN

A 26-week randomized, open-label, active controlled, parallel-group, study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferases
ANCOVA:	analysis of covariance
ARAC:	Allergic Reaction Assessment Committe
AST:	aspartate aminotransferases
ATC:	anatomical therapeudic chemical
BID:	twice daily
BMI:	body mass index
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CSR:	clinical study report
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
FRC:	fixed ratio combination
FSH:	follicle-stimulating hormone
GLP-1:	glucagon-like peptide 1
GLP-1 RA:	glucagon-like peptide 1 receptor agonist
HbA1c:	glycosylated hemoglobin A1c
HDL:	high-density lipoprotein
HLGT:	high level group term
HLT:	high level term
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent-to-treat
KM:	Kaplan-Meier
LDL:	low-density lipoprotein
LLN:	lower limit of normal
LLOQ:	lower limit of quantification
LLT:	lower level term
LOCF:	last observation carried forward
LPLV:	Last Patient Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
MMRM:	mixed-effects model with repeated measures
N:	number of availabe observations
NIMP:	non-investigational medicinal product

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OAD:	oral anti-diabetic drug
OC:	observed cases
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetic
PPG:	post-prandial plasma glucose
PSAC:	Pancreatic Safety Assessment Committe
PT:	preferred term
QD:	once daily
QW:	once weekly
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SE:	standard error
SGLT2:	sodium-glucose co-transporter-2
SMPG:	self - monitored plasma glucose
SOC:	systerm organ class
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

The study is an open-label, 1:1 randomized, active-controlled, 2-arm, 26-week treatment duration, parallel group multinational and multicenter Phase 3b study comparing

- Insulin glargine/lixisenatide fixed ratio combination (FRC) group;
- Glucagon-like peptide-1 (GLP-1) receptor agonist group.

At the end of the 26-week randomized treatment period, patients from the FRC group will be invited to participate in a 26-week single arm extension period.

The study comprises 4 periods (please see graph in Section 1.4 and flowchart in Appendix D): (1) an up-to 2-week screening period; (2) a 26-week open-label randomized treatment period; (3) a 26-week single-arm extension period and (4) a post treatment safety follow-up period (patients who prematurely discontinue the study treatment will continue in the study up to the scheduled date of study completion).

At the end of screening period, eligible patients are centrally randomized (using permuted block randomization schedule) via IRT in a 1:1 ratio to 1 of the 2 treatment groups. The patients will be stratified by value of HbA1c at screening (<8%, ≥8%) and GLP-1 receptor agonist subtype at screening (once (QD)/twice daily (BID) formulations, once weekly (QW) formulations).

It is planned to randomize a total of approximately 500 patients (250 patients per group).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of the FRC versus GLP-1 receptor agonist in HbA1c change from baseline to Week 26.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To assess the effects of the FRC versus GLP-1 receptor agonist over 26 weeks on:
  - Percentage of patients reaching HbA1c targets,
  - Fasting plasma glucose (FPG),
  - 7-point self-monitoring plasma glucose (SMPG) profile,

- Glycemic control in relation to a meal as evaluated by 2-hour Post-prandial Plasma Glucose (PPG) and glucose excursion during a standardized meal test,
- Body weight,
- To assess the safety and tolerability in each treatment group.

1.2.3 Other objectives

- To assess insulin glargine and lixisenatide doses in the combination group;
- To assess the development of anti-insulin antibodies (FRC group);
- To assess the development of anti-lixisenatide antibodies (FRC group);
- To assess the total plasma concentration of lixisenatide before and following injection (FRC group).

1.2.4 Objectives of the extension period

- To evaluate safety, efficacy, other endpoints and PK of FRC up to Week 52.

1.3 DETERMINATION OF SAMPLE SIZE

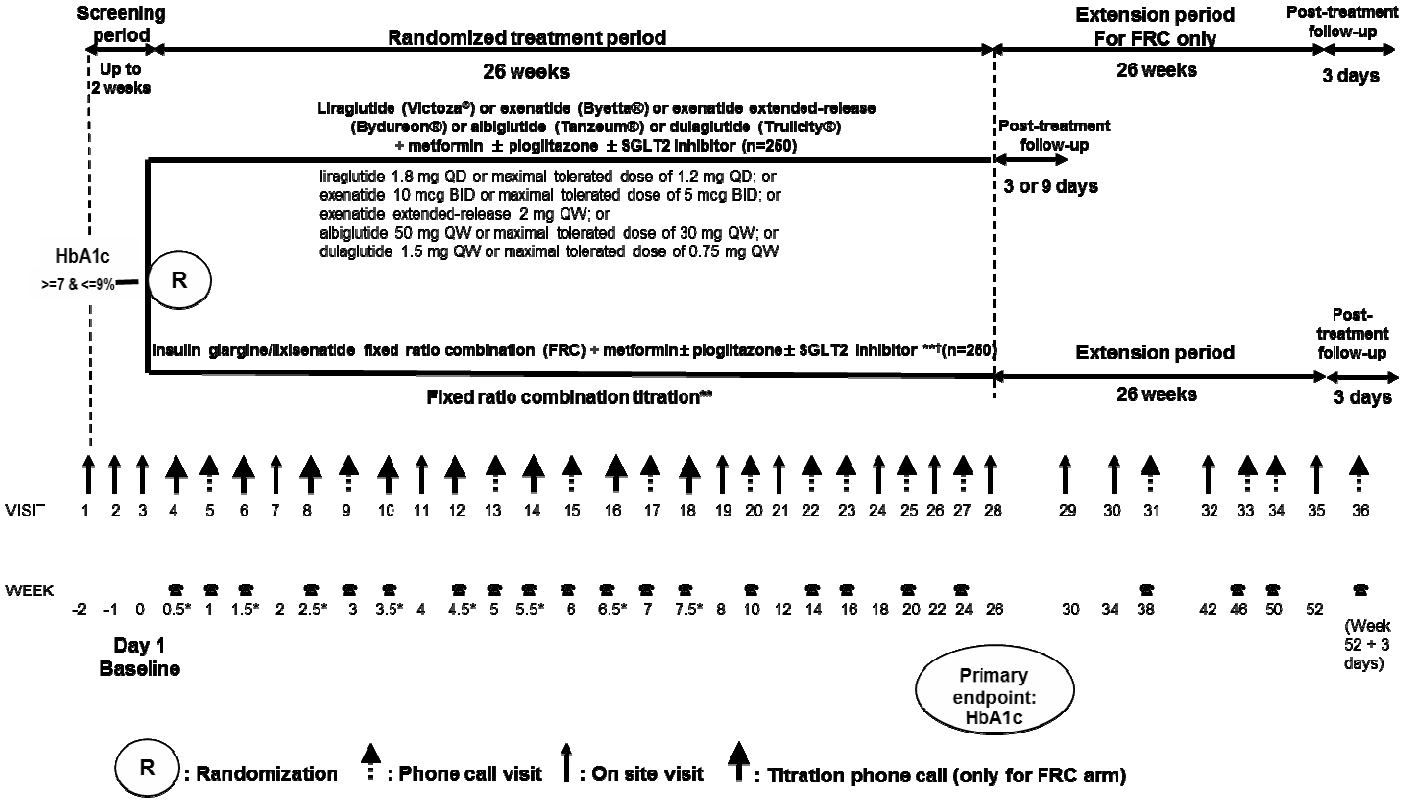
The sample size calculations are based on the primary efficacy variable change in HbA1c from baseline to Week 26 and ITT analysis, with the following assumptions:

- A common standard deviation of 1.1%,
- A 0.4% mean difference between FRC and GLP-1 receptor agonist in change in HbA1c from baseline to Week 26,
- A drop-out rate of 20%. The patients in the FRC group who discontinued treatment are assumed to respond the same as the control patients, i.e., no treatment difference between the patients in the FRC group who discontinued treatment and the control patients
- A t-test at a 2-sided 5% significance level with at least 90% power.

Based on the above assumptions, 500 patients (250 per group) are needed for this study.

Calculations were made using nQuery Advisor® 7.0.

1.4 STUDY PLAN



* Additional titration phone calls – only for FRC arm

** Insulin glargine/lixisenatide fixed ratio combination (FRC) treatment will be initiated with the Peach Pen. The initial daily dose to be administered will be 10 U: this corresponds to an initial associated dose of insulin glargine 10 U and lixisenatide 5 µg according to the 2 U/1 µg fixed ratio used in the Peach Pen. Afterwards, doses will be individually titrated throughout the study to reach and maintain fasting SMPG: 80-100 mg/dL (4.4-5.6 mmol/L) avoiding hypoglycemia.

† Liraglutide, exenatide, albiglutide, or dulaglutide is discontinued at visit 3 for patients randomized to the FRC treatment. Any patient treated with a **once weekly GLP-1 RA** upon entering the study who is assigned to receive the FRC treatment should not receive their first dose until at least 1 week after their last dose of GLP-1 RA.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

The first patient was enrolled on 25 July 2016.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	22-Sep-2016	Corrections	In determination of sample size, the mean difference between FRC and GLP-1 receptor agonist corrected to "0.4%";
1	22-Sep-2016	Modification of demographic and baseline characteristic following team's decision	Age categories updated as <50, ≥50 to <65, ≥65 to < 75, ≥75 years of age; Details of Race classification removed; Baseline diabetic microvascular complications updated to remove "including the most recent event categories"; Added 7-point SMPG baseline value at each of the 7 time points Removed physical examination and included it in Medical or surgical history. Added process for identification of medical history of cardiovascular and cerebrovascular events and medical history of allergies (i.e., relevant "preferred term" identified by medical and coding teams);
1	22-Sep-2016	Modification of concomitant medications, IMP exposure and compliance in consideration of Weekly formulation	Concomitant medications defined as those the patient continued or started on or after the first dose of open-label IMP up to 9 days after the last injection of weekly IMP; Post-treatment medications defined as those the patient continued or started on or after 10 days after the last injection of weekly IMP; Formula for calculating the duration of weekly IMP exposure updated as date of the last open-label IMP injection – date of the first open-label IMP injection + 7 days; Formula for calculating the compliance of QW IMP updated as (Total number of weeks with IMP injection/Planned number of weeks with IMP injection) x 100.

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Amendment Number	Date Approved	Rationale	Description of statistical changes
1	22-Sep-2016	Addition or modification of analyses following the change of study period and addition of endpoints	The following disposition of patients added: • The pharmacokinetic (PK) population; • Patients who have completed the whole study treatment period including 26-week extension period; • Patients who discontinued the IMP during the whole study treatment period, and the reasons for treatment discontinuation. Definition of Pharmacokinetic population added; Duration of treatment exposure modified and extended to 364 days; Added Week 22 in the MMRM model for primary efficacy analysis For FRC group, descriptive statistics added for the change of HbA1c from baseline over time by visit, all secondary efficacy endpoints and selected other endpoints for the whole study period including the extension period; Analyses of PK parameters added; For FRC group, summary of safety results added for the whole study period including the extension period, as appropriate; Analysis of anti-drug antibody variables added.
1	22-Sep-2016	The position of health authorities regarding the handling of missing data has been evolved. They have concern that only using data from the on-treatment period for subjects that either received rescue medication or had their last IMP prior to Week 26 will likely not reflect their true response at the primary endpoint, and they now recommended using all measurements of the primary endpoint obtained during the study including those collected after IMP discontinuation or rescue medication introduction for the primary analysis.	Definition of mITT updated to remove the condition “received at least one dose of investigational medicinal product”; Primary efficacy analyses for both primary and secondary efficacy endpoints performed using assessment collected during the study (including those obtained after IMP discontinuation or introduction of rescue therapy) instead of during the on-treatment period;

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	22-Sep-2016	Updates of sensitivity analyses on primary efficacy endpoint following the change in the primary analysis	ANCOVA analysis with missing data imputed by LOCF removed The following sensitivity analyses modified or added: • MMRM model using all post baseline measurement changed to use on-treatment measurements; • The statistical model for analysis of 26-week completers changed from ANCOVA to MMRM; • ANCOVA analysis added with missing data at Week 26 imputed with respect to jump to control under MNAR assumption.
1	22-Sep-2016	Modification and addition of subgroup analyses for primary efficacy endpoint	The following subgroup factors added or modified to treatment- by subgroup analysis: • Age group (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age); • Country MMRM analyses added to estimate within-group treatment effect for the anti-lixisenatide antibody status, anti-insulin glargine antibody status and anti-lixisenatide antibody concentration subgroups.
1	22-Sep-2016	Modification of definition of TEAE following the change of on-treatment definition	Definition of treatment-emergent AEs updated as AEs that developed or worsened (according to the Investigator's opinion) or became serious during the period from the administration of first dose of the study treatments up to 3 days (9 days for the weekly GLP1) after the last administration.
1	22-Sep-2016	IMPs are injected either with pens or with autoinjectors	Terminology: "Pen"-related event questionnaire replaced with "Device"-related event questionnaire
1	22-Sep-2016	Addition of database lock definitions following the change of study period	Definition of database lock updated to the following: It is planned to lock the database approximately 4 weeks after Last Patient Last Visit of the randomized treatment period (26 weeks). It is further planned to lock the database approximately 4 weeks after Last Patient Last Visit of the single-arm extension period (extension by further 26 weeks).

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Amendment Number	Date Approved	Rationale	Description of statistical changes
2	12-May-2017	Addition of demographic and baseline characteristics	The following baseline characteristics added: • Percentage of patients who used SGLT2 inhibitor at screening (data from e-CRF); • Daily dose of SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) at baseline (if used).

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan (SAP) history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

The first patient was randomized on 25 July 2016. No formal interim analysis for efficacy is planned for this study.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	29-Jun-2016	Modification and Addition of other endpoints	**2.1.3.3 Other endpoint (s)** • Insulin glargine and lixisenatide doses at Week 26 in the FRC group (for insulin absolute value and body weight adjusted); • Percentage of patients reaching the fasting SMPG target (≤ 100 mg/dl) at Week 26 in the FRC group. • Percentage of patients with no weight gain at Week 26
1	29-Jun-2016	Modification of diabetic history summary following team's decision	**2.1.1 Demographic and baseline characteristics** • Baseline diabetic microvascular complications (Yes, No) (ie, diabetic retinopathy, diabetic proliferative retinopathy, diabetic neuropathy, and diabetic nephropathy);
1	29-Jun-2016	Addition of subgroup factor for accessing the primary endpoint	**2.4.4.1 Analysis of primary efficacy endpoint(s)** Assessment of treatment effect by subgroup • Country
1	29-Jun-2016	Updates of multiplicity graph	**2.4.4.3 Multiplicity issues** Add test number in Figure 1
1	29-Jun-2016	Addition of efficacy analyses on other endpoints following the change of other endpoints	**2.4.4.4 Additional efficacy analysis(es)** Number and percentage of patients at scheduled visits (using OC) by pen type (Peach 2:1, Olive 3:1) will be provided. Patients' pen use status during the study treatment period will be summarized. The following categorical variables will be summarized using count and percentage by treatment group. • Percentage of patients with no body weight gain at Week 26. For the FRC group, count and percentage of patients reaching the fasting SMPG target (≤ 100 mg/dl) at Week 26 will be summarized.
1	29-Jun-2016	Updates on efficacy analysis	**2.1.3 Efficacy populations** Definition of mITT was updated to remove the condition "received at least one dose of IMP"

SAP version number	Date approved	Rationale	Description of statistical changes
			Definition of baseline value was updated to add "or the last available value on or before the date of randomization if not treated with open-label IMP". **2.4.4 Analyses of efficacy endpoints** Primary efficacy analyses for primary, secondary and other efficacy endpoints will be performed using assessment collected during the study (including those obtained after IMP discontinuation or rescue medication) instead of during the on-treatment period.
1	29-Jun-2016	Updates of sensitivity analyses on primary efficacy endpoint following the change in the primary analysis	**2.4.4.1 Analysis of primary efficacy endpoint(s)** The following sensitivity analysis was removed: • ANCOVA analysis with missing data imputed by LOCF The following sensitivity analyses were modified or added: • MMRM model using all post baseline measurements was changed to use on-treatment measurements; • The statistical model for analysis of 26-week completers was changed from ANCOVA to MMRM. • ANCOVA analysis was added with missing data at Week 26 imputed with respect to jump to control under MNAR assumption.
1	29-Jun-2016	Updates of sensitivity analyses on secondary efficacy endpoint following the change in the primary analysis	**2.4.4.2 Analysis of secondary efficacy endpoints** Sensitivity analyses using all post baseline measurements was changed to use on-treatment measurements
1	29-Jun-2016	Updates of additional efficacy analyses	**2.4.4.4 Additional efficacy analysis(es)** Except for IMP dose and pen related summaries, descriptive summaries using assessments collected during the study and during the on-treatment period were added.
1	29-Jun-2016	Addition of baseline variables for C-peptide	**2.1.1 Demographic and baseline characteristics** C-peptide under 30 minutes and 1-hour postprandial conditions were added.
2	09-Jan-2017	Modification of study design following the change of study period	**1.1 Study design and randomization** The study comprises 4 periods by adding a 26-week single-arm extension period.[a]
2	09-Jan-2017	Addition of other objectives following the change of study period and endpoints	**1.2.3 Other objectives** • To assess the development of anti-insulin antibodies (FRC group); [a] • To assess the development of anti-lixisenatide antibodies (FRC group); [a] To assess the total plasma concentration of Lixisenatide before and following injection (FRC group);[a]

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SAP version number	Date approved	Rationale	Description of statistical changes
			1.2.4 Objectives of the extension period To evaluate safety, efficacy, other endpoints and PK of FRC up to Week 52.[a]
2	09-Jan-2017	Updates the classification of race and ethnicity according to FDA guidance published on September 2005	**2.1.1 Demographic and baseline characteristics** Categories of race modified as: American Indian or Alaska Native, Asian/Oriental, Black, Native Hawaiian or Other Pacific Islander, White, Other. Categories of ethnicity modified as: Hispanic or Latino, Not Hispanic or Latino, Unknown
2	09-Jan-2017	Modification of rescue therapy	**2.1.2.1 Concomitant diabetes therapy** Basal insulin suggested as rescue therapy for patients in the GLP-1 RA arm [a]
2	09-Jan-2017	Modification of on-treatment definition for efficacy and safety analyses following the change of study duration	**2.1.3 Efficacy endpoints** • For patients who are not eligible to enter the extension period, the 26-week on-treatment period is defined as - For patients receiving daily IMP: the time from the first injection of open-label daily IMP up to 14 days for HbA1c; 0 day for standardized meal test parameters, 7-point SMPG and insulin glargine dose; 1 day for FPG; and 3 days for body weight after the last injection of IMP or up to the introduction of rescue therapy, whichever is the earliest. - For patients receiving weekly IMP: the time from the first injection of open-label weekly IMP up to 20 days for HbA1c; 6 day for standardized meal test parameters, 7-point SMPG and insulin glargine dose; 7 day for FPG; and 9 days for body weight after the last injection of IMP or up to the introduction of rescue therapy, whichever is the earliest.[a] • For patients who are eligible to enter the extension period, the 26-week on-treatment period is defined as the time from the first injection of open-label IMP up to V28/Week 26 visit (or Day 183 if V28/Week 26 visit is missing), or up to the introduction of rescue therapy, whichever is the earliest. [a] The on-treatment period of the whole study including the 26-week single-arm FRC extension period for efficacy variables is defined as the time from the first injection of open-label IMP up to 14 days for HbA1c; 0 day for standardized meal test parameters, 7-point SMPG and insulin glargine dose; 1 day for FPG; and 3 days for body weight after the last injection of IMP or up to introduction of rescue therapy, whichever is the earliest.[a]

SAP version number	Date approved	Rationale	Description of statistical changes
			2.1.4 Safety endpoints • For patients who are not eligible to enter the extension period, the 26-week on-treatment period is defined as For patients receiving daily IMP: time from the first injection of open-label daily IMP up to 3 days (1 day for symptomatic hypoglycemia) after the last injection of daily IMP, regardless of the introduction of rescue therapy. - For patients receiving weekly IMP: time from the first injection of open-label weekly IMP up to 9 days (7 day for symptomatic hypoglycemia) after the last injection of weekly IMP, regardless of the introduction of rescue therapy. [a] • For the patients who are eligible to enter the extension period, the 26-week on-treatment period is defined as the time from the first injection of open-label IMP up to V28/Week 26 visit (or Day 183 if V28/Week 26 visit is missing).[a] • The on-treatment period for the whole study (including the 26-week single-arm extension period) is defined as the time from the first injection of open-label IMP up to 3 days (1 day for symptomatic hypoglycemia) after the last injection of IMP, regardless of the introduction of rescue therapy. For patients who are not eligible to enter the extension period, the on-treatment period for the whole study is the 26-week on-treatment period.[a]
2	09-Jan-2017	Modification of secondary endpoints	**2.1.3.2 Secondary efficacy endpoint** Percentage of patients requiring rescue therapy during the 26 week treatment period was moved from other endpoint to secondary endpoint.[a]
2	09-Jan-2017	Addition of PK and immunogenicity endpoints	**2.1.3.3 Other endpoint (s)** **2.1.5 Pharmacokinetic variables** Pharmacokinetic parameters (FRC group): total plasma concentrations of lixisenatide added[a] **2.1.4 Safety endpoints** **2.1.4.8 Immunogenicity variables** Immunogenicity (antibody variables, FRC group): anti-insulin and anti-lixisenatide antibodies added. [a]
2	09-Jan-2017	Modification and addition of summary tables for patient disposition following the change of study	**2.2 Disposition of patients** The following summary tables were modified or added: • Patients who have completed the whole study treatment period including 26-week single-arm

SAP version number	Date approved	Rationale	Description of statistical changes
		duration	extension period • Patients who permanently discontinued the IMP during the 26-week randomized treatment period, and the reasons for treatment discontinuation. • Patients who permanently discontinued the IMP during the 26-week single-arm extension period, and the reasons for treatment discontinuation (for FRC group only). KM plots of the cumulative incidence of open-label IMP discontinuation due to any reason or due to AE for the whole study was added
2	09-Jan-2017	Modification of randomization and drug allocation irregularities following the Unify standard process	**Section 2.2.1 Randomization and drug dispensing irregularities** Randomization and drug allocation irregularities table was removed
2	09-Jan-2017	Addition of PK population definition following the addition of PK data	**Section 2.3.3 Pharmacokinetic population** Definition of pharmacokinetic population added: all randomized and treatment patients who contribute with at least one valid plasma analysis of lixisenatide[a].
2	09-Jan-2017	Modification of IMP exposure following the change of study duration	**Section 2.4.3.1 Extent of investigational medicinal product exposure** Duration of IMP exposure categories modified. For FRC group, the exposure parameters for the whole study treatment period added.
2	09-Jan-2017	Addition of compliance rates following the change of study duration	**Section 2.4.3.2 Compliance** Added compliance rate during the 26-week single-arm extension period
2	09-Jan-2017	Addition of efficacy analysis following the change of study duration	**Section 2.4.4 Analyses of efficacy endpoints** Summary statistics for the whole study period including the single-arm extension period added for all efficacy endpoints[a].
2	09-Jan-2017	Modification of efficacy analysis following the change of efficacy analysis approach	Week 26 (using LOCF) removed in summary statistics by visit.
2	09-Jan-2017	Modification of primary endpoint analysis	**Section 2.4.4.1 Analysis of primary efficacy endpoints** Week 22 was added in the MMRM model[a]. MMRM model by anti-lixisenatide/anti-insulin glargine antibody status and anti-lixisenatide antibody concentration were added[a]

SAP version number	Date approved	Rationale	Description of statistical changes
2	09-Jan-2017	Addition of safety analyses following the change of study duration	**Section 2.4.5 Analyses of safety data** Summary of safety results were added for FRC group for the whole study treatment period including the 26-week single-arm extension period.
2	09-Jan-2017	Addition of symptomatic hypoglycemia analyses following the addition of immunogenicity data	**Section 2.4.5.1 Analyses of symptomatic hypoglycemia** Summary of frequency and incidence rate in patient years for documented symptomatic hypoglycemia by anti-lixisenatide/anti-insulin glargine antibody status was added.
2	09-Jan-2017	Modification of SOC according to the introductory guide MedDRA version 19.1 published on September 2016	**Section 2.4.5.2 Analyses of adverse events** "Product issues" added to SOC
2	09-Jan-2017	Addition of device-related events analyses	For FRC group, added summary of the number (%) of patients who have device-related events with Lixisenatide dose < 5µg, > 20 µg within the corresponding time window of device-related event.
2	09-Jan-2017	Addition of anti-drug antibody analyses following the addition of immunogenicity data	**Section 2.4.5.7 Analyses of anti-drug antibody variables** The following analyses of antibody variables were added. • List and summary of number (%) of patients by antibody status by visit, as well as % of conversion from negative to positive status from baseline to Week 26 and Week 52. • For anti-insulin glargine antibodies, summary of number (%) of patients with cross-reactivity to human insulin by visit in anti-insulin glargine positive patients • For anti-lixisenatide antibodies, summary of number (%) of patients with cross-reactivity to GLP-1 and glucagon by visit in anti-lixisenatide antibody positive patients. • Descriptive statistics of antibody levels (titer or concentration), as well as respective percentage changes from baseline for anti-insulin glargine antibodies.
2	09-Jan-2017	Addition of pharmacokinetic analyses following the addition of pharmacokinetic data	**Section 2.4.6 Analyses of pharmacokinetic variables** Summary of total lixisenatide plasma concentrations of patients in the FRC group by visit and by anti-lixisenatide antibody status were added.
2	09-Jan-2017	Modification of database lock following the change of study	**Section 4 Database lock** Database lock approximately 4 weeks after the LPLV of the single-arm extension period was added.

SAP version number	Date approved	Rationale	Description of statistical changes
		duration	
2	09-Jan-2017	Modification of medical algorithm for rescued patients/rescue medication use following the change of rescue therapy	**Appendix B Definition and medical algorithm for "rescued patients" / rescue medication use** Criteria 2 was modified as "additional insulin (short/rapid-acting insulin or basal insulin) is given for ≤ 10 days".
3	This version	Addition of demographic and baseline characteristics	**Section 2.1.1 Demographic and baseline characteristics** *b* The following baseline characteristics added: • Percentage of patients who used SGLT2 inhibitor at screening (data from e-CRF); • Daily dose of SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) at baseline (if used).
3	This version	Modification of demographic and baseline characteristics	**Section 2.1.1 Demographic and baseline characteristics** *b* The following medical history and medical findings removed: • Medical history of cardiovascular and cerebrovascular events; • Medical history of allergies.
3	This version	Addition of subgroup analysis in primary efficacy endpoint	**Section 2.4.4.1 Analysis of primary efficacy endpoint(s)** The following subgroup analysis added: • SGLT2 inhibitor use (Y, N) at screening (if each category contains sufficient number of patients).
3	This version	Addition of subgroup analysis in symptomatic hypoglycemic event	**Section 2.4.5.1 Analyses of symptomatic hypoglycemia** The summary of frequency and incidence rate in patient years for documented symptomatic hypoglycemia by SGLT2 inhibitor use (Y, N) at screening (if each category contains sufficient number of patients) added.

a Change made in Protocol Amendment 1 dated 22-Sep-2016

b Change made in Protocol Amendment 2 dated 09-Jan-2017

ANCOVA = analysis of covariance; FDA = US Food and Drug Administration; HbA1c: glycosylated hemoglobin A1c; IMP = investigational medicinal product; LOCF = last observation carried forward; MMRM: mixed-effect model with repeated measures; PK = pharmacokinetic;

(electronic 3.0)

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the first injection of open-label investigational medicinal product (IMP) or the last available value on or before the date of randomization if not treated with open-label IMP. Baseline safety variables will be presented along with the on-treatment summary statistics for safety endpoints in Section 2.4.5. Derived parameters will be computed by the sponsor.

Demographic characteristics

Demographic characteristics to be summarized are:

- Age (years) derived as: (Date of informed consent - Date of birth)/365.25;
- Age categories (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age);
- Gender (Male, Female);
- Race (American Indian or Alaska Native, Asian/Oriental, Black, Native Hawaiian or Other Pacific Islander, White, Other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown);
- HbA1c (%) at Visit 1 (Week -2);
- Baseline BMI (kg/m^2) derived as: (Weight in kg)/(Height in meters)^2;
- Baseline BMI level (<30, ≥30kg/m^2);
- Randomization strata of HbA1c (<8%, ≥8%) at screening visit 1 (Week -2);
- Randomization strata of GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening;
- Country.

Medical history and medical findings

- Medical or surgical history (including physical examination abnormality);
- Subject family allergy history;
- Alcohol habits within the last 12 months;
- Smoking habits.

Medical and surgical history will be coded to a "lower level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)", and associated primary "system organ class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Disease history includes:

- Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25;
- Age at onset of diabetes (years) derived as: (Date of diagnosis of diabetes – Date of birth + 1)/365.25;
- Duration of GLP-1 receptor agonist treatment (years) derived as: (Date of informed consent – Date of first dose of GLP-1 receptor agonist + 1)/365.25;
- Percentage of patients with GLP-1 receptor agonist use by type [QD/BID formulations (Victoza® or Byetta®), QW formulations (Bydureon®, Tanzeum®, or Trulicity®)] at screening;
- Daily dose of GLP-1 receptor agonist (Victoza® or Byetta®) at baseline, or weekly dose of GLP-1 receptor agonist (Bydureon®, Tanzeum, or Trulicity®) at baseline;
- Percentage of patients who used pioglitazone at screening (data from e-CRF);
- Percentage of patients who used SGLT2 inhibitor at screening (data from e-CRF);
- Duration of metformin treatment (years) derived as: (Date of informed consent – Date of first dose of metformin + 1)/365.25;
- Daily dose of metformin (mg) at baseline;
- Daily dose of pioglitazone (mg) at baseline (if used);
- Daily dose of SGLT2 inhibitor (canagliflozin, empagliflozin or dapagliflozin) at baseline (if used);
- Categorized daily dose of metformin at baseline (<1500, ≥1500 to <2500, ≥2500 to <3000, ≥3000 mg);
- Baseline diabetic microvascular complications (Yes, No) (ie, diabetic retinopathy, diabetic proliferative retinopathy, diabetic neuropathy, and diabetic nephropathy);
- Baseline urine albumin/creatinine ratio categories (<30 mg/g [Normal], ≥30 to <300 mg/g [Microalbuminuria], and ≥300 mg/g [Macroalbuminuria]);
- Estimated Glomerular Filtration Rate (eGFR) at screening (ml/min/1.73m^2);
- eGFR categories at screening (<15 ml/min/1.73m^2 [End stage renal disease], ≥15 to <30 ml/min/1.73m^2 [Severe decrease in GFR], ≥30 to <60 ml/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 ml/min/1.73m^2 [Mild decrease in GFR], and ≥90 ml/min [Normal]).

Baseline efficacy variables

The baseline efficacy variables include:

- HbA1c;
- During standardized meal test:
  - 2-hour postprandial plasma glucose (PPG) and glucose excursion;
  - C-peptide under fasting (30 minutes prior to the meal test before IMP administration if IMP is injected before breakfast), just before the start of the standardized meal (0 minute), 30 minutes, 1-hour, 1.5-hour, and 2-hour postprandial conditions;

  Note: 2-hour plasma glucose excursion= 2-hour post prandial plasma glucose value – plasma glucose value obtained 30 minutes prior to the start of meal and before IMP administration if IMP is injected before breakfast. C-peptide under 1.5-hour postprandial condition is only for patients enrolled after the approval of Protocol Amendment 1.
- 7-point (average and each time point) SMPG;
- Body weight;
- Fasting plasma glucose (by central laboratory).

Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All anti-diabetic medications taken within 6 months prior to the screening visit or during study are to be reported in the case report form pages. All other medications taken within 3 months prior to the screening visit or during study are to be reported in the case report form pages.

All medications will be coded using the version of World Health Organization-Drug Dictionary (WHO-DD) currently in effect at Sanofi at the time of database lock.

Medications will be classified into the following 3 groups:

- Prior medications are those the patient took prior to the first injection of open-label IMP. Prior medications can be discontinued before first IMP injection or can be ongoing during treatment period.
- Concomitant medications are those the patient continued or started on or after the first injection of open-label IMP up to 3 days after the last injection of daily IMP or 9 days after the last injection of weekly IMP.
- Post-treatment medications are those the patient continued or started on or after 4 days after the last injection of daily IMP or 10 days after the last injection of weekly IMP.

A given medication can be classified in several groups.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.2.1 Concomitant diabetes therapy

Background OADs (metformin, pioglitazone and SGLT2 inhibitors) are the non-investigational background therapies authorized during the study. Rapid acting insulin (insulin glulisine when available) for patients in the FRC arm or basal insulin for patients in the GLP-1 RA arm, are the non-investigational rescue therapies suggested during the study.

Previous treatment with metformin, pioglitazone (if taken) and SGLT2 inhibitor (if taken) are to be continued throughout the study. For metformin, it should be at a stable dose of at least 1500 mg/day or maximal tolerated dose for at least 3 months prior to screening (V1). The dose of pioglitazone (if applicable) and SGLT2 inhibitors (if applicable) should also be stable for at least 3 months prior screening visit (V1). Background OAD treatment should be kept at a stable dose throughout the study unless there is a specific safety issue related to this treatment. Metformin, pioglitazone (if applicable) and SGLT2 inhibitor (if applicable) treatment dose changes are to be properly reported in patient record and in the electronic case report form (eCRF).

If rescue therapy is needed, this should be started as a single daily administration to be given as follows:

- In the FRC arm:
  - Rescue therapy is recommended only if further dose titration is not possible, i.e., the patient is already at the maximum daily dose of 60 units;
  - Rapid acting insulin (insulin glulisine when available) is suggested and should be started as a single daily administration to be given at the main meal of the day (excluding breakfast);
  - Basal insulin is not allowed in the FRC arm.
- In the GLP-1 RA arm:
  - Suggested rescue therapy is basal insulin at the investigator's discretion.

No other concomitant antidiabetic treatments except rescue therapy should be used in this study. Short time uses (≤10 days) of short/rapid-acting insulin therapy (eg, due to acute illness or surgery) will not be considered as rescue therapy.

2.1.2.2 Prohibited concomitant therapy

The following drugs are not permitted during the screening period and the treatment period:

- Any glucose-lowering agents other than the IMP, authorized background OADs and rescue therapy, if necessary,

  Note: Short time uses (≤10 days) of short/rapid-acting insulin due to acute illness or surgery (eg, infectious disease) is allowed;

- Systemic glucocorticoids for more than 10 days (topical or inhaled applications are allowed),
- Body weight loss drugs.

After the last administration of IMP during the study period, any anti-diabetic treatments (other than GLP-1 receptor agonists) are permitted, as deemed necessary by the Investigator.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

All scheduled efficacy measurements collected during the study will be used in the analysis, including those obtained after IMP discontinuation or introduction of rescue therapy.

For sensitivity analyses, the 26-week on-treatment period is defined as follows:

- For patients who are not eligible to enter the extension period, the 26-week on-treatment period is defined as
  - For patients receiving daily IMP: the time from the first injection of open-label daily IMP up to 14 days for HbA1c; 0 day for standardized meal test parameters, 7-point SMPG and insulin glargine dose; 1 day for FPG; and 3 days for body weight after the last injection of IMP or up to the introduction of rescue therapy, whichever is the earliest.
  - For patients receiving weekly IMP: the time from the first injection of open-label weekly IMP up to 20 days for HbA1c; 6 days for standardized meal test parameters, 7-point SMPG; 7 days for FPG; and 9 days for body weight after the last injection of IMP or up to the introduction of rescue therapy, whichever is the earliest.
- For patients who are eligible to enter the extension period, the 26-week on-treatment period is defined as the time from the first injection of open-label IMP up to V28/Week 26 visit (or Day 183 if V28/Week 26 visit is missing), or up to the introduction of rescue therapy, whichever is the earliest.

The on-treatment period of the whole study including the 26-week single-arm FRC extension period for efficacy variables is defined as the time from the first injection of open-label IMP up to 14 days for HbA1c; 0 day for standardized meal test parameters, 7-point SMPG and insulin glargine dose; 1 day for FPG; and 3 days for body weight after the last injection of IMP or up to introduction of rescue therapy, whichever is the earliest.

The baseline value for efficacy endpoints is the last available value prior to the first injection of open-label IMP or the last available value on or before the date of randomization if not treated with open-label IMP.

HbA1c, FPG, and parameters from the 2-hour standardized meal test are measured in a central laboratory (see study flowchart in Appendix D).

Efficacy variables will be summarized in both standard international units and conventional units when applicable.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is change in HbA1c (%) from baseline to Week 26.

2.1.3.2 Secondary efficacy endpoint(s)

Continuous secondary efficacy endpoints

The continuous secondary efficacy endpoints are:

- Change in FPG from baseline to Week 26,
- Change in 7-point SMPG profiles from baseline to Week 26 (each time point and average daily value),
- Change in 2-hour PPG and in blood glucose excursion during standardized meal test from baseline to Week 26,
- Change in body weight from baseline to Week 26,

7-point SMPG profiles will be analyzed based on the average of the glucose values recorded on eCRF on 2 different days in the week prior to the scheduled visits.

For 7-point SMPG profiles, the mean daily (ie, average on 7 points) change from baseline to Week 26 will be analyzed. In addition, the change from baseline to Week 26 for each of the 7 points will be evaluated, respectively.

For FPG, only values assessed in fasting condition will be analyzed.

Categorical secondary efficacy endpoints

The categorical secondary efficacy endpoints are:

- Percentage of patients reaching HbA1c ≤6.5% (49 mmol/mol) at Week 26,
- Percentage of patients reaching HbA1c <7% (53 mmol/mol) at Week 26.
- Percentage of patients requiring rescue therapy during the 26-week randomized treatment period.

2.1.3.3 Other endpoint(s)

- Insulin glargine and lixisenatide doses at Week 26 in the FRC group (for insulin absolute value and body weight adjusted);

- C-peptide evaluation during standardized meal test from baseline to Week 26;
- Percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) with no body weight gain from baseline to Week 26.
- Percentage of patients reaching the fasting SMPG target (≤ 100 mg/dl) at Week 26 in the FRC group.
- Percentage of patients with no weight gain at Week 26.
- Pharmacokinetics parameters (FRC group): Total plasma concentrations of lixisenatide will be assessed in the time frame from 1 to 4 hours post-injection at Day 1 of the treatment phase and prior to injection as well as in the time frame from 1 to 4 hours post injection at Week 4, Week 12, Week 26.
- Insulin glargine doses will be analyzed based on the doses recorded on eCRF and lixisenatide doses will be derived based on the insulin glargine doses and pen information.
- An algorithm for defining patients requiring rescue therapy is provided in Section 2.5.8.
- For the percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) with no body weight gain at Week 26, "no weight gain" will be defined as negative change or no change from baseline to Week 26.

For further details on missing data handling, see Section 2.5.3.

2.1.4 Safety endpoints

The safety endpoints are assessed by:

- Symptomatic hypoglycemia (documented, probable, severe symptomatic hypoglycemia),
- Adverse events (AEs), serious adverse events (SAEs), and AE of special interest (AESI),
- Safety laboratory values,
- Vital signs,
- Electrocardiogram (ECG).
- Immunogenicity (antibody variables, FRC group): anti-insulin and anti-lixisenatide antibodies.

Observation period

The observation period of safety data will be divided into 3 segments:

- The pre-treatment period is defined as the time between the date of the informed consent and the first injection of open-label IMP,
- The on-treatment period of the whole study for daily formulation is defined as the time from the first injection of open-label IMP up to 3 days (1 day for symptomatic hypoglycemia) after the last injection of IMP, regardless of the introduction of rescue

therapy. The on-treatment period of the whole study for weekly formulation is defined as the time from the first injection of open-label IMP up to 9 days (7 day for symptomatic hypoglycemia) after the last injection of IMP, regardless of the introduction of rescue therapy.

- The 26-week on-treatment period is defined as follows:
  - For patients who are not eligible to enter the extension period, the 26-week on-treatment period is defined as
    - For patients receiving daily IMP: time from the first injection of open-label daily IMP up to 3 days (1 day for symptomatic hypoglycemia) after the last injection of daily IMP, regardless of the introduction of rescue therapy.
    - For patients receiving weekly IMP: time from the first injection of open-label weekly IMP up to 9 days (7 day for symptomatic hypoglycemia) after the last injection of weekly IMP, regardless of the introduction of rescue therapy.
  - For the patients who are eligible to enter the extension period, the 26-week on-treatment period is defined as the time from the first injection of open-label IMP up to V28/Week 26 visit (or Day 183 if V28/Week 26 visit is missing).
- The post-treatment period is defined as the time starting 4 days (2 days for symptomatic hypoglycemia) after the last injection of open-label daily IMP, or starting 10 days (8 days for symptomatic hypoglycemia) after the last injection of open-label weekly IMP (after the on-treatment period of the whole study).

The on-study observation period is defined as the time from the first injection of open-label IMP until the end of study (defined as last protocol planned visit or the resolution/stabilization of all serious AEs and AEs with pre-specified monitoring as defined in the protocol).

The baseline value for safety endpoints will be the last available value prior to the first injection of open-label IMP.

2.1.4.1 Symptomatic hypoglycemia

Symptomatic hypoglycemia will be identified as events recorded on the dedicated eCRF "Symptomatic hypoglycemia" page, and will be categorized as follows (see study protocol for further details):

Severe symptomatic hypoglycemia

Severe symptomatic hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness, or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others.

Note that "requires assistance" means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Severe symptomatic hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All events of seizure, unconsciousness, or coma must be reported as SAEs.

In the eCRF, severe symptomatic hypoglycemia is identified based on information captured in the "Symptomatic hypoglycemic event information" page as those

- ticked "Subject was Not Capable of Treating Self and Required Assistance" to the question "Countermeasure Administration" and
- ticked at least one "Yes" to the question "Symptoms".

Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). Clinical symptoms that are considered to result from a hypoglycemic episode can include (but are not limited to): increased sweating, nervousness, asthenia, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and coma.

In the eCRF, documented symptomatic hypoglycemia is identified based on information captured in the "Symptomatic hypoglycemic event information" page as those

- ticked "Subject Treated Self" or "Subject was Capable of Treating Self but Received Assistance" to the question "Countermeasure Administration" and
- ticked at least one "Yes" to the question "Symptoms" and
- with a measured plasma glucose value ≤70 mg/dL (3.9 mmol/L).

Probable symptomatic hypoglycemia

Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose.

In the eCRF, probable symptomatic hypoglycemia is identified based on information captured in the "Symptomatic hypoglycemic event information" page as those

- ticked “Subject Treated Self” or “Subject was Capable of Treating Self but Received Assistance” to the question “Countermeasure Administration” and
- ticked at least one “Yes” to the question “Symptoms” and
- ticked “Oral carbohydrate”, “Intravenous glucose” or “Glucagon injection” to the question “Was Any Countermeasure Given for the Hypoglycemic Event?” and
- ticked “Yes” to the question “Did this countermeasure lead a significant improvement or prompt recovery?” and
- with no plasma glucose value,

Symptomatic hypoglycemia events fulfilling the criteria of a SAE will also be recorded on AE and SAE forms in eCRF.

2.1.4.2 Adverse events variables

Adverse event observation period

- Pre-treatment adverse events are AEs that developed or worsened or became serious from the signed informed consent date up to first injection of open-label IMP.
- Treatment-emergent adverse events are AEs that developed or worsened (according to the Investigator’s opinion) or became serious during the period from the administration of first dose of the study treatment up to 3 days (9 days for the weekly GLP1) after the last administration.
- Post-treatment adverse events are AEs that developed or worsened or became serious during the post-treatment period.

All AEs (including SAEs and AEs with prespecified monitoring) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Record the occurrence of AEs (including SAEs and AEs with prespecified monitoring) from the time of signed informed consent until the end of the study.

AESI, AE requiring specific monitoring, or specific AEs to be analyzed:

- Local tolerability at injection site: identified by searching the term “injection site” in either the PTs coded from the investigator reported terms or the PTs coded from the Allergic Reaction Assessment Committee (ARAC) diagnosis terms.
- Allergic or allergic-like reactions: events recorded on the AE form for “suspected allergic reaction” and its associated complementary forms. Allergic reaction or possible allergic reaction will be adjudicated by the ARAC.
- Increased pancreatic enzymes > 2 x ULN/suspected pancreatitis: all events confirmed by a repeated test recorded on the AE form for “increased lipase and/or amylase greater than 2 x

ULN" and its associated complementary forms. All events reported will be sent to Pancreatic Safety Assessment Committee (PSAC) for adjudication of pancreatitis.

- Pancreatic neoplasm: All pancreatic neoplasm related events (AEs of pancreas carcinoma, AEs of pancreas neoplasm benign or malignant AEs of pancreas neoplasm unspecified, AEs of pancreatic endocrine neoplasm/carcinoma, or AEs of pancreas mass, cyst, pseudocysts) will be reviewed, assessed and adjudicated by the PSAC for pancreatic neoplasm.
- Increased calcitonin ≥20 pg/mL: events recorded on the AE form for "increased calcitonin" and its associated complementary form.
- Increased ALT: events recorded on the AE form for "ALT increase" and its associated complementary form.
- Device related events reported on eCRF "Device-related events questionnaire".

Pregnancy and overdose are included in overall AE summaries if any.

2.1.4.3 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the on-treatment period
- Death post-study: deaths occurring after the end of the study

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis (including hematology and clinical chemistry) and urinalysis (albumin/creatinine ratio). Clinical laboratory values will be summarized in both standard international units and conventional units.

The laboratory data will be collected at designated visits (see study flowchart in Appendix D. The following laboratory data will be measured at a central laboratory and used as safety endpoints:

- Hematology
  - Red blood cells, platelets: hemoglobin, hematocrit, red blood cells (erythrocytes) count, platelets count.
  - White blood cells: white blood cells count, and differential counts (neutrophils, lymphocytes, monocytes, basophils, and eosinophils).
- Clinical chemistry
  - Lipid parameters: total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides.
  - Pancreatic enzymes: lipase, amylase.

- Serum calcitonin.
- Electrolytes: sodium, potassium, calcium, phosphorus.
- Renal function: creatinine, calculated creatinine clearance, uric acid.
- Liver function: alanine aminotransferases (ALT), aspartate aminotransferases (AST), alkaline phosphatase (ALP), total bilirubin (and, in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).

- Urine analysis: albumin/creatinine ratio.

For triglycerides, only values assessed in fasted patients will be analyzed.

Other laboratory data not mentioned above (pregnancy test, serum follicle-stimulating hormone [FSH], hepatitis screen, and urinalysis) will not be defined as safety endpoints (collected at screening only as per study flowchart in Appendix D, except for pregnancy test which is also performed during study).

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include supine heart rate (bpm) and systolic and diastolic blood pressures (mmHg) in seated position.

2.1.4.6 Physical examination

Any abnormality related to physical examination will be reported in the eCRF "Adverse Event" page.

2.1.4.7 Electrocardiogram variables

ECGs are measured automatically by the device from the investigator as automatic 12-lead ECG. ECG status of "normal" or "abnormal" will be reported in the eCRF as determined by the Investigator.

2.1.4.8 Immunogenicity variables

Antibody variables in FRC group:

- Anti-insulin glargine antibody:
  - Status (Positive, Negative) and titer;
  - Cross-reactivity of anti-insulin glargine antibodies with human insulin.
- Anti-lixisenatide antibody:
  - Status (Positive, Negative) and concentration;

- Cross-reactivity of anti-lixisenatide antibodies with GLP-1 and glucagon as well as neutralizing effects of these antibodies against lixisenatide, GLP-1 and glucagon.

The on-treatment period for antibody variables is defined as the time from the first injection of open-label IMP up to 28 days after the last injection of open-label IMP.

2.1.5 Pharmacokinetic variables

Pharmacokinetics variables include total plasma concentrations of lixisenatide for FRC group.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as all patients who have signed the informed consent.

Randomized patients consist of all patients who have signed informed consent, with a randomized open-label treatment kit allocated and recorded in the IRT database, regardless of whether the treatment kit was actually used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report (CSR), using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who have completed the 26-week randomized treatment period as per protocol
- Patients who have completed the whole study treatment period including 26-week single-arm extension period
- Patients who permanently discontinued the IMP during the 26-week randomized treatment period, and the reasons for treatment discontinuation.
- Patients who permanently discontinued the IMP during the 26-week single-arm extension period, and the reasons for treatment discontinuation (for FRC group only).
- Patients who completed/discontinued the study,
- Patients' end of study status (completed, not completed) by end of treatment status (completed, not completed),

- Status at last study contact.

For the screened, screen failure, and non-randomized but treated patients, percentages will be calculated using the number of screened patients as the denominator. All other categories of patients will be presented by treatment group, and percentages will be calculated using the number of randomized patients within each treatment group as the denominator. Reasons for treatment discontinuation will be provided in tables giving numbers and percentages by treatment group.

A summary of the distribution of patients by country and center will also be provided (overall number of patients screened, screened but not randomized, randomized, and randomized but not treated, and number of patients randomized and discontinued from study treatment for each treatment group).

Patients treated but not randomized, patients randomized but not treated and patients randomized but not treated as randomized will be identified and described in separate listings. Only the patients of the third category (randomized and not treated as randomized) will be part of efficacy and safety analyses (see Section 2.3). Safety data of patients treated but not randomized will be reported separately.

The randomization strata [HbA1c at Visit 1 (<8%, ≥8%) and GLP-1 receptor agonist subtype at screening (QD/BID fomulations, QW formulations)] assigned by IRT will be summarized. The percentages will be calculated using the number of randomized patients as the denominator. The discrepancy between the strata assigned by IRT and the information reported on eCRF will be listed for all randomized patients.

Kaplan-Meier (KM) plots of the cumulative incidence of open-label IMP discontinuation due to any reason or due to AE will be provided for the 26-week randomized treatment period. Additionally, a listing of these patients, along with the reason for discontinuation, will be provided. Time to treatment discontinuation will be defined as the number of days from the first injection of open label IMP until the day of treatment discontinuation. All completers will be considered as censored observations. The censoring time will be the number of days from the first injection of open-label IMP until the last injection date during 26-week randomized treatment period. Similar KM plots and listing of patients will also be provided for the whole study including 26-week single-arm extension period (FRC group only).

All major or critical deviations will be listed and summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the analysis populations for efficacy, safety defined in Section 2.3 will be summarized in a table by number of patients on the randomized population:

- Efficacy population: modified intent-to-treat (mITT) population,
- Safety population.
- PK population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the CSR. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized (patients who received open-label IMP without calling the IRT or before calling the IRT, or patients who did not give their informed consent) will not be considered as randomized. They will be excluded from any population for analysis, including efficacy and safety. However, if these patients experience any safety event, they will be presented and listed separately in the appendix of the CSR.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Efficacy populations

The mITT population will be the primary population for efficacy analyses. For efficacy analyses, patients will be analyzed in the treatment group to which they were randomized by the IRT, irrespective of the treatment actually received.

2.3.1.1 Modified intent-to-treat population

The mITT population consists of all randomized patients who have both a baseline assessment and at least 1 post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures. Patients will be analyzed for efficacy analyses according to the treatment group to which they are randomized.

2.3.2 Safety population

The safety population consists of all randomized patients who receive at least 1 dose of open-label IMP (regardless of the amount of treatment administered). Patients will be analyzed for safety analyses according to the treatment actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately;
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized;
- When a patient is exposed to both FRC and GLP-1 receptor agonist, the patient will be analyzed in the treatment group (FRC or GLP-1 receptor agonist) in which he/she is treated longer;
- Patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study medication.

2.3.3 Pharmacokinetic population

- For pharmacokinetic (PK) analyses, the PK population is defined as all randomized and treated patients who contribute with at least one valid plasma analysis of lixisenatide.

2.4 STATISTICAL METHODS

In general, descriptive statistics of quantitative efficacy and safety endpoints (result and change from baseline) by scheduled visit will be provided on observed cases (OC), ie, only including patients having a non-missing assessment at a specific visit.

Continuous data will be summarized by treatment group using the number of available observations (N), mean, SD, minimum, median, and maximum.

Categorical data will be summarized by treatment group using counts and percentages. Missing data will not be categorized in the summaries.

2.4.1 Demographics and baseline characteristics

No statistical test will be performed for the between-group difference on demographic and baseline characteristics (including medical history and baseline efficacy data).

Demographic and baseline disease characteristics, baseline efficacy variables and medical history and medical findings (see Section 2.1.1) will be summarized with appropriate descriptive statistics by treatment group and overall. Pathologies associated with past medical or surgical history will be summarized by primary SOC and HLT, with events sorted by primary SOC in internationally agreed order and decreasing frequency of HLT in the overall group. These summaries will be provided on randomized patients, using the treatment group to which they were randomized.

2.4.2 Prior or concomitant medications

Summaries of prior, concomitant and post-treatment medications will be presented on randomized patients for each treatment group (and overall for the summary of prior medications), using counts and percentages. No statistical test for the between-group difference will be performed.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). A given medication can be classified in several groups. All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication, therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of anatomic class followed by therapeutic class, based on the overall incidence across treatment groups. In case of equal frequency regarding anatomic classes (respectively therapeutic classes), alphabetical order will be used.

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency of anatomic class followed by therapeutic class, based on the incidence in the FRC group. In case of equal frequency regarding anatomic classes (respectively therapeutic classes), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment received within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of open-label IMP exposure will be assessed by the duration of IMP exposure during the study.

The duration of treatment exposure will be the total number of days of administration of the open-label IMP, regardless of unplanned intermittent discontinuations.

The duration of daily IMP exposure will be calculated as:

(Date of the last open-label IMP injection – Date of the first open-label IMP injection) + 1.

The duration of weekly IMP exposure will be calculated as:

(Date of the last open-label IMP injection – Date of the first open-label IMP injection) + 7.

Duration of IMP exposure (days) will be summarized using continuous descriptive statistics (N, mean, SD, minimum, median, and maximum). The cumulative exposure in patient years, defined as the sum of patients' duration of IMP exposure, will also be provided. In addition, duration of IMP exposure will be summarized categorically by counts and percentages for each of the following categories, and cumulatively according to these categories:

- 1 to 14 days,
- 15 to 28 days,
- 29 to 56 days,
- 57 to 84 days,
- 85 to 126 days,
- 127 to 168 days,
- 169 to 182 days,
- 183 to 210 days,
- 211 to 238 days,
- 239 to 294 days,
- 295 to 364 days
- > 364 days.
- The exposure parameters are provided for the 26-week randomized treatment period and for the whole study treatment period (FRC group only), respectively.

2.4.3.2 Compliance

Overall treatment compliance is defined as the actual number of days with IMP injection compared to the planned number of days with IMP injection during the open-label treatment period, up to treatment discontinuation. It is calculated according to the following formula:

- For QD/BID formulations,

$$\text{Compliance rate (\%)} = \left[\frac{\text{Total number of days with IMP injection}}{\text{Planned number of days with IMP injection}}\right] \times 100$$

- For QW formulations,

$$\text{Compliance rate (\%)} = \left[\frac{\text{Total number of weeks with IMP injection}}{\text{Planned number of weeks with IMP injection}}\right] \times 100$$

Treatment compliance will be summarized by treatment group using continuous descriptive statistics (N, mean, SD, median, and minimum, and maximum). In addition, the percentage of patients who have <60%, ≥60% to <80%, ≥80% to ≤100%, and >100% compliance will be summarized by treatment group.

The compliance parameters are provided for the 26-week randomized treatment period and for the 26-week single-arm extension period (FRC group only), respectively.

For calculating compliance rate during the 26-week single-arm extension period, the following formula will be used.

$$\text{Compliance rate (\%)} = \left[\frac{\text{Total number of days with IMP injection during extension period}}{\text{Planned number of days with IMP injection during extension period}}\right] \times 100$$

Date of the first IMP injection during extension period is equal to the date of first IMP administration with a daily dose > 0 after the date of administration reported on the eCRF "Treatment Status" page.

Cases of overdose (see study protocol for further details) will constitute AEs and be analyzed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

Efficacy analyses will be performed on the mITT population using efficacy assessment collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy, unless otherwise specified.

For a patient to be included in a change from baseline analysis (endpoint – baseline) or a baseline adjusted analysis of an endpoint, the patient must have both a baseline and a post-baseline measure for that endpoint.

2.4.4.1 Analysis of primary efficacy endpoint(s)

The statistical test will be 2-sided tests at a nominal 5% significance level.

Primary analysis

The primary efficacy endpoint (change in HbA_{1c} from baseline to Week 26) will be analyzed using a mixed-effect model with repeated measures (MMRM) under the missing at random framework. The MMRM model will include treatment group (FRC or GLP-1 receptor agonist), randomization strata of HbA_{1c} (<8%, ≥8%) at V1 (week -2), randomization strata of GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening, visit (week 8, week 12, week 18, Week 22 and Week 26), treatment-by-visit interaction and world region as fixed effects, and baseline HbA_{1c} value-by-visit interaction as the covariates. The adjusted mean change in HbA_{1c} from baseline to Week 26 for each treatment group will be estimated in the framework of this model, as well as the between group difference in LS means and the corresponding 95% CI.

The MMRM model will be implemented using SAS® (Version 9.4 or higher) MIXED procedure (PROC MIXED) with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degree of freedom will be estimated using the Kenward-Roger approximation by fitting values from post-randomization scheduled visits in the 26-week randomized treatment period. This model will use only scheduled HbA_{1c} measurements.

Primary analysis will be performed using the mITT population and including all scheduled HbA1c measurements collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

Sensitivity analyses

The following sensitivity analyses will be performed for the primary endpoint:

- The same MMRM model as described in the primary analysis will also be performed by including only the scheduled HbA1c measurements collected during the 26-week on-treatment period (see Section 2.1.3).
- A sensitivity analysis will also be conducted on the 26-week completers in mITT population (ie, all mITT patients who completed the 26-week open-label randomized treatment period and did not start any rescue therapy before the end of the 26 week randomized treatment period) using the observed Week 26 values and the same MMRM model as described above.
- To investigate the impact of rescue therapy, the same MMRM model as described in the primary analysis will be performed by excluding the measurements after receiving the rescue therapy. The analysis includes all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation, but excluding those obtained after introduction of rescue therapy.
- In order for patients with missing data to be adequately represented by the patients with data, a sensitivity analysis using multiple imputations with respect to jump to control under the MNAR assumption will be performed. In particular,

- For patients in the GLP1-RA group who have no HbA1c values at Week 26, the missing data will be considered as missing at random. Missing HbA1c values in this situation will be imputed by the regression method using the observed data from GLP-1 RA group. The regression imputation model will include baseline HbA1c values and randomization strata.
- For patients in the FRC group who have no HbA1c value at Week 26, the missing HbA1c values will be imputed using baseline HbA1c values, randomization strata and coefficients generated from the regression model in the GLP-1 RA group plus an error. The error term will be randomly drawn from normal distribution with mean zero and a standard deviation. The standard deviation of the normal distribution will be calculated from pooled standard error of the regression model in the GLP-1 RA group and the standard error of the regression model in the FRC group. The regression model in the FRC group will be generated using the observed data from FRC group and will include baseline HbA1c values and randomization strata.

Missing HbA_{1c} values at Week 26 will be imputed 100 times to generate 100 data sets with complete HbA1c values at Week 26. The change from baseline to Week 26 will be derived from observed and imputed HbA1c values at this time point. The completed data sets will be analyzed using an ANCOVA model with treatment groups, randomization strata, and world region as factors and the baseline HbA1c value as a covariate. The results from the 100 analyses will be combined using SAS PROC MIANALYZE.

Assessment of treatment effect by subgroup

Descriptive analyses will be performed on the primary endpoint to summarize the treatment effects across subgroups defined by the following baseline or screening factors:

- Race (American Indian or Alaska Native, Asian/Oriental, Black, Native Hawaiian or Other Pacific Islander, White, Other) (any category with less than 5 patients may be combined with another category as appropriate);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Age group (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age) (any category with less than 5 patients may be combined with another category as appropriate);
- Gender;
- Baseline BMI level (<30, ≥30 kg/m^2);
- GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening
- Baseline HbA_{1c} (<8%, ≥8%);
- Pioglitazone use (Yes, No) at screening;
- SGLT2 inhibitor use (Yes, No) at screening (if each category contains sufficient number of patients);
- World region.

- Country

The treatment effects across the subgroups defined for each of these factors will be estimated for the change from baseline to Week 26 in HbA_{1c} in the mITT population, and using the MMRM approach with treatment group (FRC or GLP-1 receptor agonist), randomization strata of HbA_{1c} (<8%, ≥8%) at V1 (week -2), randomization strata of GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening visit, subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor, and world region as fixed effects, and using the baseline HbA_{1c} value-by-visit interaction as a covariate. The adjusted estimates of treatment mean differences (FRC versus GLP-1 receptor agonist) with standard errors and 95% CIs will be provided as appropriate across the subgroups.

In case that the subgroup factor is identical or similar to a randomization strata factor (eg, baseline HbA_{1c} category and GLP-1 RA category), only the subgroup factor will be included in the model in order to avoid collinearity issue in the analysis. In case that the subgroup factor is country, the world region will not be included in the model.

A similar MMRM model will also be used to estimate the within-group treatment effect for the change from baseline to Week 26 in HbA1c for the following subgroups:

- Anti-lixisenatide antibody status (positive, negative) at the end of 26-week treatment;
- Anti-insulin glargine antibody status (positive, negative) at the end of 26-week treatment;
- Anti-lixisenatide antibody concentration at the end of 26-week treatment: <lower limit of quantification (LLOQ), ≥ LLOQ to 100 nmol/L, > 100 nmol/L.

If the antibody measurement is not available at Week 26, the LOCF procedure will be used by taking the last available post-baseline antibody measurement as the value at Week 26.

The adjusted means for each treatment group will be provided across the subgroups as appropriate, as well as the associated standard errors and 95% confidence intervals.

Summary statistics at scheduled visits

Summary statistics (for screening value, baseline value, observed values, and observed changes from baseline) at scheduled visits (using OC) will be provided for each treatment group. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits (using OC). These analyses will be performed using efficacy assessments obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

- Similar presentations will be provided for patients who have completed the 26-week treatment period. In addition, summary statistics tables will be presented using HbA1c assessments obtained during the 26-week on-treatment period (see Section 2.1.3).

- Similar summary statistics and graphical presentations will also be provided for FRC group for the whole study period including the extension period.

2.4.4.2 Analyses of secondary efficacy endpoints

For secondary efficacy endpoints included in the multiplicity procedure described in Section 2.4.4.3, 2-sided statistical tests for the superiority of FRC over GLP-1 receptor agonist will be performed at the alpha level of 0.05.

Except for 2-hour PPG and glucose excursion, all continuous secondary efficacy endpoints at Week 26 defined in Section 2.1.3.2 will be analyzed using the same MMRM approach as described in Section 2.4.4.1 to compare FRC with GLP-1 receptor agonist. The analyses include all scheduled measurements collected during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy. This model will include fixed effect terms including treatment group (FRC or GLP-1 receptor agonist), randomization strata of HbA_{1c} (<8%, ≥8%) at V1 (week -2), randomization strata of GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening, scheduled visit, treatment-by-visit interaction, and world region, and the covariate of baseline value-by-visit interaction. Means and adjusted means of each treatment group will be provided, as well as adjusted mean and associated two-sided 95% CI of the differences between treatment groups. The statistical tests for between-group differences will be two-sided at the alpha level of 0.05.

2-hour PPG and glucose excursion, for which only 1 post-baseline assessment is scheduled, will be analyzed using ANCOVA with the missing data at Week 26 imputed by LOCF to compare FRC with GLP-1 receptor agonist. This model will include fixed effect terms including treatment group (FRC or GLP-1 receptor agonist), randomization strata of HbA_{1c} (<8%, ≥8%) at V1 (week -2), randomization strata of GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening, and world region, and a covariate using the corresponding baseline value. Means and adjust means of each treatment group will be provided, as well as adjusted mean and associated two-sided 95% CI of the difference between treatment groups. The LOCF procedure will be used by taking the last available post-baseline measurement collected during the 26-week randomized treatment period as the value at Week 26.

Summary statistics (for screening value, baseline value, observed values, and observed changes from baseline) at scheduled visits (using OC) will be provided for each treatment group for continuous secondary efficacy endpoints. Each summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits (using OC).

All categorical secondary efficacy endpoints defined for 26-week randomized treatment period in Section 2.1.3.2 will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata of HbA_{1c} (<8%, ≥8%) at visit 1(week -2) and randomization strata of GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening. The proportion in each treatment group will be provided, as well as the difference of proportions between groups

with associated 2-sided 95% CI. For the categorical secondary endpoints in which HbA1c is assessed at Week 26, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or introduction or rescue therapy. If no assessment is available at Week 26 at all, patients will be treated as failures (non-responders).

For HbA1c responders (≤6.5%, <7%), summary tables and graphs will be provided by treatment group at scheduled visits (using OC). For between-group comparison, a sensitivity analysis will be performed excluding patients whose HbA1c values at baseline are ≤6.5% (for the ≤6.5% responder analysis) or <7% (for the 7% responder analysis). The summary by visit may also be provided excluding those patients.

A KM curve will be provided by treatment group for the cumulative incidence of rescue therapy during the 26-week randomized treatment period and during the whole study period including the extension period (FRC group only). A listing will be provided for rescued patients.

For all continuous secondary endpoints, only descriptive statistics will be provided for the FRC group at the scheduled visits for the whole study period including the extension period. For all the categorical secondary endpoints defined for the extension period, counts and percentages will be summarized for FRC group using all data available at Week 52, with patients having data missing at Week 52 treatment as non-responders.

Sensitivity analysis

Sensitivity analyses will be performed for the following variables using scheduled measurements collected during the 26-week on-treatment period (excluding those collected after introduction of rescue therapy) (see Section 2.1.3). Continuous variables will be analyzed using MMRM or ANCOVA depending on the variables as specified earlier in Section 2.4.4.2. Categorical variables will be analyzed using CMH method as described earlier. For the categorical variables in which HbA1c is assessed at Week 26, patients will be treated as failures (non-responders) if they have no assessment during the on-treatment period, including those who discontinue study treatment before Week 26, start rescue therapy before Week 26, or have no on-treatment assessment at all in mITT population.

- Change in 2-hour PPG and in glucose excursion during the standardized meal test from baseline to Week 26,
- Change in the daily average of the 7-point SMPG from baseline to Week 26 (each time point and average daily value),
- Change in FPG from baseline to Week 26,
- Change in body weight from baseline to Week 26,
- Percentage of patients reaching HbA1c ≤ 6.5 % at Week 26,
- Percentage of patients reaching HbA1c < 7 % at Week 26.

2.4.4.3 Multiplicity issues

To control the Type I error, a step-down testing procedure (please see Figure 1) will be applied.

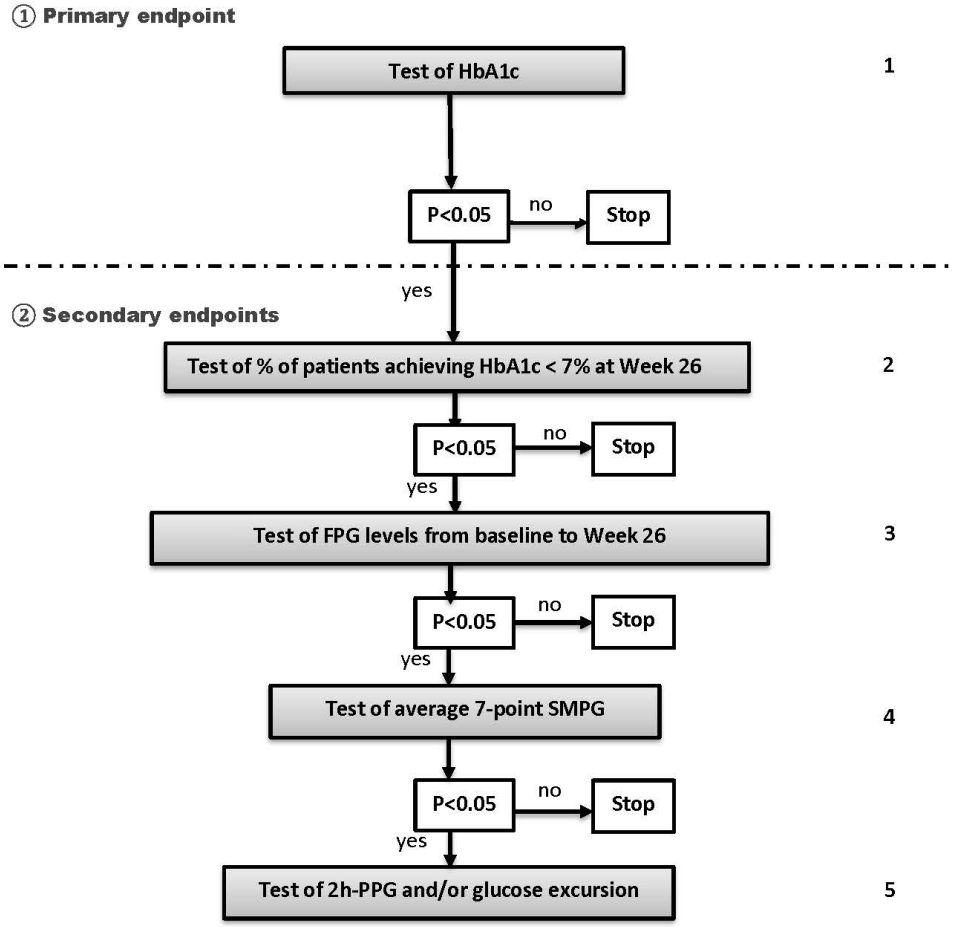
For the primary efficacy endpoint (change from baseline to Week 26 in HbA_{1c}), no multiplicity adjustment is needed to control the Type I error since only one comparison of FRC versus GLP-1 receptor agonist will be performed.

If the primary variable is statistically significant at the 5% level, a hierarchical testing procedure will be performed to test the following secondary efficacy variables in the following prioritized order. Testing will stop when an endpoint is found not to be statistically significant at the 5% level:

1. Percentage of patients reaching HbA_{1c} <7% at Week 26.
2. Change in FPG from baseline to Week 26.
3. Change in the daily average of the 7-point SMPG from baseline to Week 26.
4. Change in 2-hour Post Prandial Glucose (PPG) and/or glucose excursion during the standardized meal test from baseline to Week 26.

Multiplicity adjustment will not be performed on the secondary efficacy variables that are not included in the above list.

Figure 1 - The step-down testing procedure



(electronic 3.0)

2.4.4.4 Additional efficacy analysis(es)

For the daily insulin glargine and lixisenatide doses, summary statistics at scheduled visits (using OC) will be provided for the FRC group. The summary will include the number of observations, mean, SD, minimum, median, and maximum. Summary statistics will also be provided for the body weight adjusted insulin glargine doses at scheduled visits (using OC). In addition, daily dose of insulin glargine at scheduled visits (using OC) will be summarized by count and percentage for each of these categories: <10 U, ≥10 U - <20 U, ≥20 U - <30 U, ≥30 U - ≤ 40U, > 40 U - ≤ 50; >50 to ≤ 60U, =60U , and > 60 U. Daily dose of lixisenatide at scheduled visits (using OC) will be summarized by count and percentage for each of these categories: <5 µg, ≥5 µg- < 10 µg, ≥10 µg- <15 µg, ≥15 µg- ≤ 20µg, = 20µg, > 20µg.

Number and percentage of patients at scheduled visits (using OC) by pen type (Peach 2:1, Olive 3:1) will be provided. Patients' pen use status during the 26-week randomized treatment period will also be summarized by count and percentage for each of these categories: No switch of pen, switch pen once from Peach 2:1 to Olive 3:1 at any time, and other patterns.

Number and percentage of patients in the FRC group will also be summarized by pen type and the dose categories described above based on the final doses of insulin glargine and lixisenatide at the end of the 26-week randomized treatment period, respectively.

For the C-peptide evaluation, summary statistics (for screening value, baseline value, observed values, and observed changes from baseline) at scheduled visits (using OC) will be provided for each treatment group. Each summary will include the number of observations, mean, SD, minimum, median, and maximum. A summary statistics table will also be presented using assessments obtained during the 26-week on-treatment period (see Section 2.1.3).

The following categorical variables will be summarized using count and percentage by treatment group.

- Percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) with no body weight gain at Week 26.
- Percentage of patients with no body weight gain at Week 26.
- Percentage of patients reaching the fasting SMPG target (≤ 100 mg/dl) at Week 26 (for the FRC group only).

For the categorical variables in which HbA1c, body weight or fasting SMPG is assessed at Week 26, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or introduction of rescue therapy. If no assessment is available at Week 26 at all, patients will be treated as failures (non-responders).

Similar summary tables will also be presented using scheduled measurements collected during the 26-week on-treatment period (see Section 2.1.3) in mITT population. Patients will be treated as failures (non-responders) if they have no such assessments during the 26-week on-treatment

period, including those who discontinue study treatment before Week 26, start rescue medication before Week 26, or have no on-treatment assessments at all in mITT population.

For the composite endpoint (HbA1c <7% with no body weight gain), a patient will be treated as a responder only if the criterion is met for each component of the composite endpoint.

For the FRC group only, selected analyses of other endpoints defined in Section 2.1.3.3 will also be performed for the whole study including the 26-week single-arm extension period (using assessment obtained during whole study and/or the on-treatment period of the whole study defined in Section 2.1.3).

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group for the 26-week randomized treatment period, unless specified otherwise. A similar summary of safety results will also be presented for FRC group for the whole study treatment period including the 26-week single-arm extension period, as appropriate.

The "observation period" defined in Section 2.1.4 are applicable for classification of AEs, (potentially clinically significant abnormality) PCSA values for the laboratory and vital sign.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately;
- The baseline value is defined as the last available value before the first injection of open-label IMP. For WBC and differential counts, the baseline will be defined as the last available value before the first injection of open-label IMP where no differential component is missing;
- The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014 [Appendix A]). PCSA criteria for parameters not cited in the protocol as safety parameters will not be analyzed;
- PCSA criteria will determine which patients had at least 1 PCSA during the specified period, taking into account all evaluations performed during the specified period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage during the specified period;
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter during the specified period by treatment group in the safety population;

- For laboratory parameters cited in the protocol as efficacy endpoints (including HbA1c and plasma glucose), PCSA summaries will not be provided. These parameters will be summarized in Section 2.4.4;
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the last on-treatment value (see Section 2.5.4);
- The analysis of the safety variables will be descriptive and no testing is planned;
- Selected safety analyses will be summarized by age group (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age), gender, race subgroups, GLP-1 receptor agonist subtype at screening, and any pertinent subgroups as appropriate.

2.4.5.1 Analyses of symptomatic hypoglycemia

Analyses of symptomatic hypoglycemia will be performed on the on-treatment period, as defined in Section 2.1.4. Unless specified otherwise, all analyses described below will be performed by treatment group for the 26-week on-treatment period and for FRC group for the on-treatment period of the whole study including the extension period, respectively.

The number (%) of patients with any symptomatic hypoglycemia recorded in the dedicated eCRF "Symptomatic hypoglycemia" page and meeting protocol definitions for severe, documented or probable symptomatic hypoglycemia described in Section 2.1.4.1 and with at least 1 symptomatic hypoglycemia by category (ie, severe, documented, and probable symptomatic hypoglycemia) will be summarized by treatment group for the on-treatment period, as well as the incidence rate in patient years. Two types of incidence rates will be presented: the number of patients with at least 1 event per patient years (calculated as the number of patients with at least 1 event / total exposure in patient years), and the number of events per patient years (calculated as the number of events / total exposure in patient years). Note: here exposure is duration of on-treatment, ie, duration of IMP treatment in days +1 for daily formulation and duration of IMP treatment in days + 7 for weekly formulation (see Section 2.1.4).

The above summary will also be provided for the on-treatment period before introduction of rescue therapy. In addition, all the above summary will be provided for documented symptomatic hypoglycemia with plasma glucose <60 mg/dL [3.3 mmol/L].

- The summary of frequency and incidence rate in patient years for documented symptomatic hypoglycemia will be provided as appropriate by gender (Male, Female), age group (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age), race (American Indian or Alaska Native, Asian/Oriental, Black, Native Hawaiian or Other Pacific Islander, White, Other), GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening, SGLT2 inhibitor use (Yes, No) at screening (if each category contains sufficient number of patients), and insulin and lixisenatide dose groups (FRC group only).
- The summary of frequency and incidence rate in patient years for documented symptomatic hypoglycemia will be provided by anti-lixisenatide and anti-insulin glargine

antibody status (Positive, Negative) during 26-week randomized treatment period and during whole study treatment period including 26-week extension period, respectively. A patient is defined as anti-lixisenatide (or anti-insulin glargine) antibody positive during the 26-week randomized treatment period (or whole study treatment period) if the patient is anti-lixisenatide (or anti-insulin glargine) antibody positive at any time during the 26-week randomized treatment period (or whole study treatment period).

The number (%) of patients with at least 1 documented symptomatic hypoglycemia during the 26-week on-treatment period will be assessed by treatment group over time, using weekly time intervals up to 26 weeks, ie, [0-1] week, (1-2] weeks, (2-3] weeks, (3-4] weeks, etc. Similar summaries will be provided for FRC group during the on-treatment period of the whole study, using weekly time intervals up to 52 weeks. In each time interval, the numerator in the calculation of percentages will be the number of patients with at least 1 event occurring in this time interval. Two types of analyses will be included: (1) only the first event will be counted for each patient and all recurrent events will not be included, and the denominator for the calculation of percentages will be the number of patients at risk at the beginning of the time interval who did not experience a first event in the preceding intervals; and (2) the recurrent events in subsequent intervals will be counted once for each patient in the numerator of the corresponding interval, and the denominator for the calculation of percentages will be the number of patients at risk at the beginning of the time interval.

A KM curve will also be provided by treatment group for the time to first documented symptomatic hypoglycemia during the on-treatment period.

The number (%) of patients with at least 1 documented symptomatic hypoglycemia during the on-treatment period, as well as the corresponding number of events, will be summarized as necessary by hour of the day for each treatment group, using the following hour intervals: ≥23:00 to <06:00, ≥06:00 to <10:00, ≥10:00 to <14:00, ≥14:00 to <18:00, ≥18:00 to <23:00.

Similar analysis may be provided for severe symptomatic hypoglycemia as appropriate.

A listing of patients for all events reported on the dedicated eCRF “Symptomatic hypoglycemia” page will be provided and sorted by the following order: (1) patients with protocol defined symptomatic hypoglycemia including severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, or probable symptomatic hypoglycemia (see Section 2.1.4.1); and (2) patients with symptomatic hypoglycemia not meeting protocol definition; and (3) patients with asymptomatic hypoglycemia.

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on treatment-emergent adverse events (TEAEs). Pre- and post-treatment AEs will be described separately. The adverse events will be summarized by treatment group for the 26-week randomized treatment period and for FRC group for the whole

study treatment period including the 26-week single-arm extension period, respectively, unless specified otherwise.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is pre- or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by primary SOC, HLGT, HLT and PT, sorted by the internationally agreed order for SOCs and alphabetic order for HLGT, HLT and PT within a SOC, for each treatment group. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by primary SOC and PT sorted by the internationally agreed order for SOCs and decreasing frequency for PTs within a SOC will define the presentation order for all other similar tables unless otherwise specified. Sorting of PTs will be based on the results for the FRC group.

The internationally agreed order of SOCs shown below was described in the Introductory Guide MedDRA Version 19.1, September 2016 International Conference on Harmonisation for SOC:

1. Infections and infestations
2. Neoplasms benign and malignant (including cysts and polyps)
3. Blood and lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic, and mediastinal disorders
14. Gastrointestinal disorders

15. Hepato-biliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal, connective tissue, and bone disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium, and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital and familial/genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury, poisoning, and procedural complications
25. Surgical and medical procedures
26. Social circumstances
27. Product issues

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any:
  - TEAE,
  - Serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation;
- All TEAEs by primary SOC, showing number (%) of patients with at least 1 TEAE, sorted by internationally agreed order of primary SOCs;
- All TEAEs by PT, showing number (%) of patients with at least 1 TEAE, sorted by decreasing incidence of PT;
- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least 1 TEAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetic order;
- All TEAEs by primary SOC and PT, showing number (%) of patients with at least 1 TEAE, sorted by SOC internationally agreed order and decreasing incidence of PTs within a SOC. This sorting order will be applied to all other similar tables, unless otherwise specified;
- Common TEAEs (PTs with an incidence ≥2% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order;

- All TEAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order;
- All TEAEs by maximal severity, presented by primary SOC and PT, showing number (%) of patients with at least 1 TEAE by severity (ie, mild, moderate, or severe), sorted by sorting order defined above;
- All TEAEs by primary and secondary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order;
- Kaplan-Meier curves will be provided, when appropriate, for the time to first onset of the following PTs: nausea and vomiting;
- The frequency of TEAEs over time will be provided for nausea and vomiting, using weekly time intervals up to 26 weeks, ie, [0-1] week, (1-2] weeks, (2-3] weeks, (3-4] weeks, etc. Similar summary will be also provided for the FRC group for the whole study treatment period including the extension period, using weekly intervals up to 52 weeks. In each time interval, the numerator in the calculation of percentages will be the number of patients with at least 1 TEAE occurring in this time interval. Two types of analyses will be included: (1) only the first event will be counted for each patient and all recurrent events will not be included, and the denominator for the calculation of percentages will be the number of patients at risk at the beginning of the time interval who did not experience a first event in the preceding intervals; and (2) the recurrent events in subsequent intervals will be counted once for each patient in the numerator of the corresponding interval, and the denominator for the calculation of percentages will be the number of patients at risk at the beginning of the time interval;
- Summaries of common TEAEs (PTs with an incidence ≥2% in any treatment group) will be provided as appropriate by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age), and race (American Indian or Alaska Native, Asian/Oriental, Black, Native Hawaiian or Other Pacific Islander, White, Other), GLP-1 receptor agonist subtype (QD/BID fomulations, QW formulations) at screening.
- Summaries of all TEAEs will be provided for FRC group respectively by anti-lixisenatide and anti-insulin glargine antibody status (Positive, Negative) during the 26-week randomized treatment period and during the whole study treatment period including 26-week extension period.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent SAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

- All treatment-emergent SAEs regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent SAEs, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 TEAE leading to treatment discontinuation, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Local tolerability at injection site

The number (%) of patients with local intolerability at injection site will be summarized by PT (PTs coded from the investigator reported terms or PTs coded from ARAC diagnosis terms), sorted by decreasing incidence of PT. Similar summaries will be provided for FRC group respectively by anti-lixisenatide and anti-insulin glargine antibody status (Positive, Negative). All events will be listed.

Allergic reactions

Kaplan-Meier curves will be provided for the time to first onset of events adjudicated as allergic reactions by ARAC. The number (%) of patients with events adjudicated as allergic reactions by ARAC will be summarized by PT (sorted by decreasing incidence of PT) and ARAC diagnosis along with 2 subcategories, events adjudicated as possibly related to IMP and events adjudicated as not related to IMP. Tabulation summaries will be provided as necessary by gender (Male, Female), age group (<50, ≥50 to <65, ≥65 to < 75, ≥75 years of age), race (American Indian or Alaska Native, Asian/Oriental, Black, Native Hawaiian or Other Pacific Islander, White, Other). Similar summaries will be provided for FRC group respectively by anti-lixisenatide and anti-insulin glargine antibody status (Positive, Negative).

All the allergic events reported by the investigator on the AE form for suspected allergic event and its associated complementary forms (confirmed or not confirmed by ARAC) will be listed.

Pancreatic-related events

- Increased pancreatic enzymes >2 times ULN
  - The number (%) of patients with events reported on the AE form for increased lipase and/or amylase >2 times ULN and its associated complementary forms will be summarized by PTs for each treatment group, sorted by decreasing incidence of PT.
  - The number (%) of patients with events positively adjudicated as pancreatitis by the PSAC will be summarized by type: 1) acute pancreatitis, 2) acute exacerbation of chronic pancreatitis, 3) chronic pancreatitis, 4) unknown pancreatitis.

- All events sent to PSAC for adjudication of pancreatitis (ie, events reported on the AE form for increased lipase and/or amylase>2 times ULN) will be listed along with the adjudication outcome.

- Pancreatic neoplasm
  - All the events sent to PSAC for adjudication for pancreatic neoplasm will be listed along with the adjudication outcome including PSAC diagnosis, type of neoplasm (malignant, benign, not determined), cancer stage etc.

Increased calcitonin

The number (%) of patients with events reported on the AE form for increased calcitonin ≥20 pg/mL and its associated complementary forms will be summarized by PTs for each treatment group, sorted by decreasing incidence of PT in the FRC group. In addition, a listing of those patients will be provided.

ALT increase

The number (%) of patients with events reported on the AE form for ALT increase and its associated complementary forms will be summarized by PT for each treatment group, sorted by decreasing incidence of PT in the FRC group. In addition, a listing of those patients will be provided.

Device-related events

The number (%) of patients with events reported on device-related event questionnaire will be summarized for each treatment group along with 2 subcategories, events associated with a clinical event (either symptomatic hypoglycemic event or adverse event) and events not associated with a clinical event. The number of events and rates in patient year will also be summarized as appropriate. The number (%) of patients who have device-related events with lixisenatide dose <5 µg, > 20 µg within the corresponding time window (from event start date to event end date or to treatment end date if event end date is missing) of device-related event will be summarized for FRC group only In addition, a listing of patients with those events will be provided.

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs in the FRC group within each SOC.
- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs in the FRC group within each SOC.

Listings

Supportive AE listings will be provided for all AEs, SAEs and AEs leading to treatment discontinuation. These listings will include at least the following information, sorted by treatment, patient identification, and onset date: treatment, patient identification, country, age, gender, race, BMI, primary SOC, PT, reported term, onset date, study day (relative day to the start date of open-label treatment), AE duration, duration of exposure, intensity, corrective treatment, action taken with IMP, date of treatment discontinuation (if relevant), relationship to IMP/NIMP/study procedures, outcome, date of death (if any), seriousness, seriousness criteria, and AE status ("Pre" for a pre-treatment AE; "T" for a TEAE; and "Post" for a post-treatment AE).

2.4.5.3 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- Deaths in nonrandomized patients or randomized but not treated patients

TEAEs leading to death (death as an outcome on the eCRF AE page as reported by the investigator) by primary SOC, HLGT, HLT, and PT, showing number (%) of patients, sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

The summaries will be provided by treatment group for the 26-week randomized treatment period and for FRC group for the whole study treatment period including the 26-week single-arm extension period, respectively.

2.4.5.4 Analyses of laboratory variables

Laboratory parameters will be grouped and summarized by biological function as described in Section 2.1.4.4. The summaries will be provided by treatment group for the 26-week randomized treatment period and for FRC group for the whole study treatment period including the 26-week single-arm extension period, respectively.

Descriptive statistics (N, mean, median, SD, minimum, and maximum) will be used to summarize results and changes from baseline of all laboratory parameters. Summaries will be presented by treatment group using baseline values, observed values from scheduled visits and last on-treatment values. In addition, descriptive statistics will also be presented separately for the post-treatment period.

The number (%) of patients with PCSAs (list provided in Appendix A) at any time during the on-treatment period will be summarized by biological function and treatment group for each laboratory parameter, except calcitonin and the albumin/creatinine ratio, whatever the baseline level and/or according to the following baseline status categories:

- Normal/Missing,
- Abnormal according to PCSA criterion or criteria.

For calcitonin and the albumin/creatinine ratio, no PCSA criterion is defined. Similar summaries using the pre-defined categories will be provided for the on-treatment period. The pre-defined categories are, for calcitonin ≤ULN, >ULN - 20 ng/L, ≥20 - <50 ng/L, and ≥50 ng/L (Note that ng/L is the standard international unit and is equivalent to pg/mL); and for albumin/creatinine ratio <30 µg/mg creatinine [Normal], ≥30 to <300 µg/mg creatinine [Microalbuminuria], and ≥300 µg/mg creatinine [Macroalbuminuria]. For calculated estimated eGFR, the classification according to Food and Drug Administration (FDA) guidance published on March 2010 will be used as the PCSA criterion: <15 mL/min/1.73m² [End stage renal disease], ≥15 to <30 mL/min/1.73m² [Severe decrease in GFR], ≥30 to <60 mL/min/1.73m² [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m² [Mild decrease in GFR], and ≥90 mL/min/1.73m² [Normal].

All measurements collected during the on-treatment period, including values from unscheduled visits, will be considered for the PCSA summaries. These summaries will include patients in the safety population who have at least 1 assessment performed during the on-treatment period. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries, and when required by the definition of the abnormality, patients must also have available laboratory normal ranges.

For some parameters, such as liver enzymes, the lower limit of normal (LLN) is not considered clinically relevant, and values below this limit are considered normal. When there are multiple PCSA criteria for a specific parameter (eg, ALT), the patient will be counted once during the on-treatment period for the specific parameter in question under the worst/maximum PCSA category.

PCSA summaries (or similar summaries using the pre-defined categories for calcitonin and albumin/creatinine ratio) will also be presented separately for the post-treatment period.

For parameters for which no PCSA criterion is defined, similar table(s) using the normal ranges will be provided.

A listing of patients with at least 1 post-baseline PCSA (or out of normal range when no PCSA criterion is defined) will be provided and will display the entire patients' profile across time for all parameters belonging to the corresponding biological function. Individual data listings will include flags when applicable:

- Baseline values will be flagged "B".
- Normal laboratory ranges, available for most laboratory parameters, will be identified as ULN and LLN. Baseline, and individual data will be flagged "L" if the value is below the LLN and will be flagged "H" if it is above the ULN.
- Laboratory PCSA criteria will be used for the corresponding laboratory parameters. Values reaching a PCSA limit will be flagged (+, ++, -, or – depending upon the direction and level of the abnormality). Flags for WBC and differential counts will be determined using data expressed in international units.

For parameters whose PCSA criteria are multiples of the ULN, the parameter's value will also be expressed as a multiple of the ULN in the individual data provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post-baseline visit will also be displayed by duration of exposure for each treatment group (only if a tabulation summary is necessary).

A listing will be provided for possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in total bilirubin >2 x ULN) with liver related TEAEs, ALT, AST, ALP, total bilirubin, and the following complementary parameters if available: conjugated bilirubin and prothrombin time/INR, creatine phosphokinase, serum creatinine, complete blood count, immunoglobin M (IgM) antibodies to Hepatitis A virus, IgM antibodies to Hepatitis B core antigen, antibodies to Hepatitis C Virus, and Hepatitis C ribonucleic acid, IgM antibodies to Cytomegalovirus, and IgM antibodies to Hepatitis E virus, auto-antibodies: anti-nuclear, anti-deoxyribonucleic acid, anti-smooth muscle, Epstein-Barr virus, herpes viruses, and anti-liver/kidney microsomes.

2.4.5.5 Analyses of vital sign variables

Descriptive statistics (N, mean, median, SD, minimum, and maximum) will be used to summarize results and change from baseline of all vital sign parameters. The summaries will be provided by treatment group for the 26-week randomized treatment period and for FRC group for the whole study treatment period including the 26-week single-arm extension period, respectively.

Summary statistics will be presented using baseline values, observed values from scheduled visits, and last on-treatment value. Mean value (±SE) at each scheduled visit will be plotted in each treatment group.

Number (%) of patients with PCSAs (see Appendix A) at any time during the on-treatment period will be summarized by treatment group for each vital sign parameter.

All measurements collected during the on-treatment period of the whole study, including values from unscheduled visits, will be considered for the PCSA summaries. The summaries will include patients in the safety population who have at least 1 assessment performed during the on-treatment period of the whole study. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries.

A listing of patients with at least 1 post-baseline PCSA will be provided and will display the patient's profile over time of all vital sign parameters. Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged (+, or - depending of the direction).

The PCSA summaries and descriptive statistics of vital sign parameters will also be presented separately for the post-treatment period.

2.4.5.6 Analyses of electrocardiogram variables

- Shift tables will be provided to present ECG status according to baseline status (Normal/Missing, Abnormal) for each treatment group during the 26-week on-treatment period and for FRC group during the on-treatment period of the whole study. Supportive listings of patients with abnormal ECG status at any post-baseline visit will be provided.

2.4.5.7 Analyses of anti-drug antibody variables

Analyses of antibody variables will be performed on the safety population (only in patients from the FRC group).

The number and percentage of patients by antibody status will be listed and summarized by visit, as well as the percentage of conversion from negative to positive status from baseline to Week 26 and Week 52. For anti-insulin glargine antibodies, the number and percentage of patients with cross-reactivity to human insulin will also be summarized by visit in anti-insulin glargine positive patients. For anti-lixisenatide antibodies, the number and percentage of patients with cross-reactivity to GLP-1 and glucagon will be summarized by visit in anti-lixisenatide antibody positive patients.

Antibody levels (titer or concentration), as well as respective percentage changes from baseline for anti-insulin glargine antibodies, will be listed and summarized by visit using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum and maximum.

2.4.6 Analyses of pharmacokinetic variables

Total plasma concentrations of lixisenatide of patients in the FRC group will be listed and summarized by visit and time window and by anti-lixisenatide antibody status in the PK population, using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum and maximum.

Population PK modeling might be pursued for exploratory purpose by the Pharmacokinetics, Disposition and Metabolism (PKDM) group at Sanofi. Results would be provided in a separate report.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Renal function formulas

The estimated glomerular filtration rate (GFR) will be calculated by 4 variable MDRD formula using the serum creatinine, race, age, and gender of the patient:

GFR (mL/min/1.73 m^2) = 175 x serum creatinine (mg/dL) $^{-1.154}$ x age (yr) $^{-0.203}$ x 1.212 [if black] x

0.742 [if female]

Calculation of LDL-C

When TG is lower than or equal to 4.52 mmol/L (400 mg/dL), LDL-C is calculated using the Friedewald equation as:

A) in mmol/L unit, total cholesterol – HDL-C – TG/2.17;

B) in mg/dL unit, total cholesterol – HDL-C – TG/5.

2.5.2 Data handling conventions for secondary efficacy variables

For patients who drop out or are rescued before the end of 26-week randomized treatment, the missing data will be handled by the statistical approach chosen. The missing data will be handled by MMRM approach, or imputed by taking the last available post-baseline measurement as the Week 26 value (see Section 2.5.4) in ANCOVA-LOCF approach.

For the categorical secondary endpoints, data handling conventions are described in Section 2.4.4.2.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Derived variables will be considered missing if any of the original variables required to calculate them are missing. For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then change from baseline at endpoint will be missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

Incomplete date of first injection

Date of first injection is the first non-missing start date of open-label IMP completed in the eCRF "Investigational medicinal product administration" module.

For patients who are randomized and dispensed a treatment kit but who are lost to follow-up just after Visit 3 (only the treatment kit number is reported in the eCRF "Investigational medicinal product administration" module without any dose information), the date of first injection will be

imputed using the Visit 3 date. When a patient is randomized but not dispensed a treatment kit, the "Investigational medicinal product administration" module should be blank. In this case, the patient will be considered as randomized but not treated, unless the patient's disposition is not confirmed.

Handling of computation of treatment duration if IMP end of treatment date is missing

For the calculation of the 26-week randomized treatment duration, the date of the last injection of randomized open-label IMP is equal to the date of last administration reported on the eCRF "Treatment Status" page. If this date is missing, the randomized exposure duration should be kept as missing. For the calculation of the treatment duration of whole study for patients participating the extension period, the date of the last injection of IMP is equal to the date of last administration reported on the eCRF "Treatment Status for Extension Phase" page. If this date is missing, the exposure duration should be kept as missing.

In the definition of the 26-week on-treatment period, the date of the last injection of open-label IMP for the patients who do not participate in the extension period is equal to the date of the last administration reported on the eCRF "Treatment Status" page. If the date of last administration reported on the eCRF "Treatment Status" page is missing, for the patients with at least 1 record where the daily dose/weekly dose is greater than zero, the date of the last open-label IMP administration in the "Dose" panel with a daily dose/weekly dose >0 or the date of the last AE reported on the eCRF "Adverse Events" page with "Action Taken with IMP" not ticked "Not Applicable", whichever is the latest will be used. For the patients who were lost to follow-up after the initial dispensation of IMP, the date of Visit 3/randomization visit will be used.

In the definition of the on-treatment period of the whole study including the 26-week single-arm extension period, the date of last injection of IMP for the patients who participate in extension period is equal to the date of the last administration reported on the eCRF "Treatment Status for Extension Phase" page. If the date of last administration reported on the eCRF "Treatment Status for Extension Phase" page is missing, for the patients with at least 1 record where the daily dose is greater than zero, the date of the last IMP administration in the "Dose" panel with a daily dose >0 or the date of the last AE reported on the eCRF "Adverse Events" page with "Action Taken with IMP" not ticked "Not Applicable", whichever is the latest will be used. The date of last injection of IMP for the patients who do not participate in extension period is the same as the date of the last injection of open-label IMP in the definition of the 26-week on-treatment period.

Handling of missing data in the calculation of average 7-point SMPG

At least 4 measurements from the 7-points profile are required for calculating the average 7-point SMPG.

Handling of missing data for categorical secondary efficacy endpoints

Please see Section 2.4.4.2.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial missing AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the on-treatment period, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of adverse events when date and time of first IMP administration is missing

When the date and time of the first IMP is missing, all AEs that occurred after or on the day of randomization and before or on the day of last dose plus 3 days for daily formulation and 9 days for weekly formulation should be considered as TEAEs. The exposure duration should be kept as missing. The last dose intake should be clearly identified in the eCRF and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to IMP/NIMP/study procedures

If the assessment of the relationship to IMP/NIMP/study procedures is missing, the relationship to IMP/NIMP/study procedures has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

Nominal post-baseline visits will be used for descriptive statistics and time course plots.

The end of treatment visit is entered as Visit 7000 in the eCRF if a patient prematurely discontinues treatment.

- If Visit 7000 occurs during 26-week randomized treatment period, Visit 7000 will be re-allocated to the next scheduled visit except for the last scheduled on-site visit (Visit 28) at the patient level if the next scheduled visit is an on-site visit but not performed.
- If Visit 7000 occurs during the 26-week single-arm extension period for FRC group, Visit 7000 will be re-allocated to the next scheduled visit except for the last scheduled on-site visit (Visit 35) at the patient level if the next scheduled visit is an on-site visit but not performed. When Visit 7000 is re-allocated to the next scheduled on-site visit at the patient level, a measurement at Visit 7000 for a given parameter will be re-allocated to the same visit only if the re-allocated visit happens to be the next scheduled visit for the given parameter.

When efficacy related parameters are analyzed by MMRM, the post baseline measurements assessed during 26-week randomized treatment period at Visit 7000, Visit 6000 (pre-rescue visit) and Visit 9900 (unscheduled visit) will be re-allocated to the closest scheduled post-baseline visit at the parameter level if the measurement for a given parameter is not available at the scheduled visit. These efficacy related parameters include HbA1c, body weight, 7-point SMPG, FPG. An analysis window will be applied to the re-allocation. In particular, the following rule will be used to determine the analysis window for a scheduled visit for each parameter:

- Lower bound = targeted day of current scheduled visit - integer part of (targeted day of current scheduled visit – targeted day of the preceding scheduled visit)/2;
- Upper bound = targeted day of current scheduled visit + integer part of (targeted day of the next scheduled visit – targeted day of current scheduled visit -1)/2;
- Lower bound for the first scheduled post-baseline visit is always Day 1 (the day of first IMP injection);
- No upper bound is specified for the last scheduled post-baseline visit.

The analysis window for HbA1c is given below for illustration.

Table 3 - Analyses window definition for HbA1c

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 8 (Visit 19)	57	1 to 70
Week 12 (Visit 21)	85	71 to 105
Week 18 (Visit 24)	127	106 to 140
Week 22 (Visit 26)	155	141 to 168
Week 26 (Visit 28)	183	169 to 210 (for patients who are eligible to enter the extension period)
		169 to . (for patients who are not eligible to enter the extension period)

Study days are calculated from the day of first IMP injection; the day of first IMP injection is Day 1.

The analysis windows for other parameters analyzed by MMRM can be obtained similarly based on their respective scheduled visits. After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. In case of equality, the earliest measurement will be used.

Reference day

The reference day for the calculation of extent of exposure, time to onset, and relative days will be the day of the first injection of open-label IMP, denoted as Day 1.

Baseline definition for efficacy/safety data

For the safety analyses, the baseline for a given parameter is defined as the last available measurement, including unscheduled assessment, assessed prior to the first injection of open-label IMP. For the efficacy analyses, the baseline for a given parameter is defined as the last available measurement, including unscheduled assessments, assessed prior to the first injection of open-label IMP or the last available value on or before the date of randomization if not treated with open-label IMP.

Efficacy endpoints at Week 26

Efficacy endpoints at Week 26 will be assessed using values measured at Visit 28 (Week 26). For ANCOVA-LOCF approach, if a patient discontinues the treatment prematurely, received rescue therapy, or does not have a measurement at Visit 28 for efficacy endpoints, the last non-missing post-baseline value, including measurements from unscheduled visits will be used as the value at Week 26.

Summary statistics by visit for continuous efficacy endpoints

Summary statistics (N, mean, SD, SE, minimum, median, maximum) of continuous efficacy endpoints (observed data and change from baseline) will be provided at scheduled visits as per protocol. Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number) and labeled with the targeted approximate day/week.

Last on-treatment value for laboratory variables and vital signs

The last on-treatment value is the final measurement assessed during the on-treatment period (26-week on-treatment period or the on-treatment period of the whole study) for safety variables, regardless of the introduction of rescue therapy, including measurements at unscheduled visits. A detailed definition of the on-treatment period is provided in Section 2.1.4.

Display of safety data by visit (laboratory variables and vital signs)

Descriptive statistics (N, mean, SD, minimum, median, maximum) of quantitative laboratory variables and vital signs (observed data and change from baseline) during the on-treatment period (26-week on-treatment period or the on-treatment period of the whole study) for all scheduled visits as per protocol will be provided (ie, only including patients having non-missing assessments at a nominal visit). In addition, these summaries will also include a row for the 'last value on-treatment' to describe the last available on-treatment value (see above). Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number) and labeled with the targeted approximate day/week.

As specified in the study protocol, laboratory data from scheduled visits are reported by central laboratories. When both central and local laboratories report values from the same blood sample (ie, sample collected at the same date and time), only measurements from the central laboratory will be included in the analyses. When only local laboratory results are reported and central laboratory results are unavailable, the local results will not be used in the efficacy analyses.

When a patient has more than 1 measurement from the central laboratory for the same laboratory parameter on the same date, the average of the measurements will be used. For the same laboratory parameter, if a patient has more than 1 measurement on different dates for the same scheduled visit, the value closest to the last open-label IMP injection prior to the scheduled visit will be used for the scheduled visit. When the values for the same scheduled visit are equidistant, the last value should be used for the scheduled visit.

Linked adverse events that worsened or became serious

An AE that worsened or became serious will have a separate record in the data from the original event record with a reference identification number that links the new record to the original record. An AE that worsened or became serious will be considered a new recurring AE in the summary of recurrent events or in the summary of events by time intervals.

2.5.5 Unscheduled visits

The determination of baseline values and values at Week 26 or Week 52 and values at the end of treatment for efficacy variables will be based on all measurements from both scheduled and unscheduled visits (measurements for central laboratories only), as mentioned in Section 2.5.4. The determination of the last on-treatment value for safety parameters will also be based on all assessments from both scheduled and unscheduled visits (see Section 2.5.4). Measurements from

unscheduled visits (including results from local laboratories when no corresponding central laboratory results are available) will also be considered for PCSA summaries of safety parameters.

Unscheduled visit measurements will not be included in the by-visit summaries.

2.5.6 Pooling of centers for statistical analyses

Center will not be included in the analysis models for efficacy. However, all centers within a region will be pooled, and region will be included as fixed effect in the MMRM or ANCOVA models for primary and secondary efficacy endpoints.

2.5.7 Statistical technical issues

None.

2.5.8 Rescued patient data

The source for the identification of rescued patients is the eCRF “Antidiabetic medications” page. Patients who met the following condition are considered “rescued”:

1. The answer to “Reason for treatment” is “Rescue therapy” in the eCRF “Antidiabetic medications” page.
2. The answer to “Reason for treatment” is not “Rescue therapy” in the eCRF “Antidiabetic medications” page, but a program which implemented a medical algorithm to search the database for anti-diabetic medication identified an anti-diabetic medication (see Appendix B)

The second condition listed above is supplemental to the first condition and is implemented to avoid the exclusion of any potential rescued patients.

3 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned for this study.

The primary analysis of the efficacy and safety are performed on the data collected during the 26-week randomized treatment period. The timing of this analysis is when the last randomized patient has completed the 26-week randomized treatment period. The results of the primary analysis will not be used to change the conduct of the ongoing study in any aspect.

4 DATABASE LOCK

It is planned to lock the database approximately 4 weeks after the Last Patient Last Visit (LPLV) of the randomized treatment period (26 weeks).

It is further planned to lock the database approximately 4 weeks after the LPLV of the single-arm extension period (extension by further 26 weeks).

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

None.