



AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: HOE901 (insulin glargine) / AVE0010 (lixisenatide) combination

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

STUDY NUMBER: EFC13794

STUDY NAME: LixiLan-G

VERSION DATE / STATUS: Approval date (12-May-2017) / Approved

NCT Number: NCT02787551

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Clinical Trial Protocol	Version number: 1 (electronic 1.0)	Date: 11-Feb-2016
Version Number: 1	EudraCT	2014-004850-32
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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR

Name:
Address:

Tel:
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E-mail:

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MONITORING TEAM'S REPRESENTATIVE

Name:
Address:

Tel:
Fax:
E-mail:

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SPONSOR

Company:
Address:

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OTHER EMERGENCY TELEPHONE NUMBERS

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CLINICAL TRIAL SUMMARY

COMPOUND: HOE901 (insulin glargine) / AVE0010 (lixisenatide) combination	STUDY No: EFC13794 STUDY NAME: LixiLan-G
TITLE	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
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	Phase III
STUDY OBJECTIVE(S)	<p>Primary objective:</p> <p>To demonstrate the superiority of the insulin glargine/lixisenatide fixed ratio combination (FRC) versus Glucagon-like peptide-1 receptor agonist (GLP-1 RA) in hemoglobin A1c (HbA1c) change from baseline to Week 26.</p> <p>Secondary objective(s):</p> <p>To assess the effects of the FRC versus GLP-1 receptor agonist over 26 weeks on:</p> <ul style="list-style-type: none"> • Percentage of patients reaching HbA1c targets; • Fasting Plasma Glucose (FPG); • 7-point Self-Monitored 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. <p>Other Objectives</p> <ul style="list-style-type: none"> • To assess insulin glargine and lixisenatide doses in the combination group; • To assess the development of anti-insulin and anti-lixisenatide antibodies (fixed ratio combination group); • To assess the total plasma concentration of lixisenatide before and following injection (fixed ratio combination group). <p>Objectives of the extension period</p> <ul style="list-style-type: none"> • To evaluate safety, efficacy, other endpoints and PK of FRC up to Week 52.

STUDY DESIGN	<p>Randomized, open label, 2 treatment-arm, 26-week treatment duration, parallel-group multinational and multicenter study comparing the FRC to GLP-1 receptor agonist, with FRC single-arm extension of 26 weeks.</p> <p>The randomization (1:1) will be stratified by values of HbA1c at screening (<8%, ≥8%) (<64 mmol/mol, ≥64 mmol/mol) and GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations).</p> <p>The study will comprise 4 periods:</p> <p>1- An up-to 2-week screening period;</p> <p>2- A 26-week open-label randomized treatment period: at V3, patients will be randomized to either receive the FRC plus metformin ± pioglitazone ± SGLT2 inhibitors or to continue on GLP-1 receptor agonist plus metformin ± pioglitazone ± SGLT2 inhibitors;</p> <p>3- A 26-week single-arm extension period</p> <ul style="list-style-type: none">• For patients treated with the FRC during the randomized period: After the end of the randomized treatment period (Week 26) patients will continue to use the FRC during the next 26 weeks of the extension period. Patients on rescue therapy during the randomized period and still having their HbA1c >8% at Week 22 will not be invited to participate in the extension period.• For patients treated with GLP1-RA during the randomized period: Patients will not be invited to participate in the extension period and will be prescribed the most appropriate antidiabetic treatment at the Investigator's discretion. <p>4- A post-treatment follow-up period:</p> <ul style="list-style-type: none">• Patients who will not participate in the extension period will perform the safety follow up visit 3 days after Week 26, except those who prematurely and permanently discontinued investigational medicinal product (IMP) administration during the randomized treatment period but continued in the study up to the scheduled date of study completion. Patients receiving weekly GLP-1 RAs will perform the safety follow-up 9 days after Week 26.• Patients who will participate in the extension period will perform the safety follow up visit 3 days after Week 52, except those who prematurely and permanently discontinue IMP administration during the extension period but continued in the study up to the scheduled date of study completion.
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<p>STUDY POPULATION</p> <p>Main selection criteria for the randomized treatment period</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none">• Patients with type 2 diabetes mellitus diagnosed at least one year prior to screening visit (V1);• Patients who have been treated with one of the following GLP-1 receptor agonists for at least 4 months prior to screening visit (V1), and with stable dose for at least 3 months prior to screening visit (V1):<ul style="list-style-type: none">- Liraglutide (Victoza®) 1.8 mg once daily (QD) or 1.2 mg QD, if 1.8 mg QD is not well tolerated according to Investigator's judgment;- or Exenatide twice daily (BID) (Byetta®) 10 µg BID or of 5 µg BID, if 10 µg BID is not well tolerated according to Investigator's judgment;in combination with metformin (daily dose ≥1500 mg/day or Maximum Tolerated Dose (MTD)), with or without pioglitazone, with or without SGLT2 inhibitor, all at stable dose for at least 3 months prior to screening; <p>or</p> <ul style="list-style-type: none">• Patients who have been treated with stable dose of one of the following GLP-1 receptor agonists for at least 6 months prior to screening visit (V1):<ul style="list-style-type: none">- Exenatide extended-release (Bydureon®) 2 mg once weekly (QW), if well tolerated according to Investigator's judgment;- Albiglutide (Tanzeum®) 50 mg QW or 30 mg QW, if 50 mg QW is not well tolerated according to Investigator's judgment;- Dulaglutide (Trulicity®) 1.5 mg QW or 0.75 mg QW, if 1.5 mg QW is not well tolerated according to Investigator's judgment.in combination with metformin (daily dose ≥1500 mg/day or MTD), with or without pioglitazone, with or without SGLT2 inhibitor, all at stable dose for at least 3 months prior to screening;• Signed written informed consent. <p>Exclusion criteria:</p> <ul style="list-style-type: none">• At screening visit (V1), age <legal age of adulthood;• Screening HbA1c <7% (53 mmol/mol) and >9% (75 mmol/mol);• Pregnancy or lactation, women of childbearing potential with no effective contraceptive method;• Any use of anti-diabetic drugs within 3 months prior to the screening visit (V1), other than those described in the inclusion criteria;• Previous treatment with insulin in the year prior to screening visit (V1) (note: short term treatment with insulin (≤10 days) due to intercurrent illness including gestational diabetes is allowed at the discretion of the study physician);• Laboratory findings at the time of screening, including:<ul style="list-style-type: none">- Fasting Plasma Glucose (FPG) >250 mg/dL (13.9 mmol/L);- Amylase and/or lipase >3 times the upper limit of the normal laboratory range (ULN);- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >3ULN;- Calcitonin ≥20 pg/mL (5.9 pmol/L);- Positive serum pregnancy test.
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	<ul style="list-style-type: none"> • Patient who has a renal function impairment with estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m² (using MDRD formula) or end-stage renal disease; • Contraindication to use of insulin glargine, or lixisenatide or GLP-1 receptor agonist (Victoza®, Byetta®, Bydureon®, Tanzeum®/ or Trulicity®) according to local labeling; • Any contraindication to metformin or pioglitazone or SGLT2 inhibitors (when applicable) use, according to local labeling; • History of hypersensitivity to insulin glargine, or to any of the excipients; • History of allergic reaction to any GLP-1 receptor agonist or to Metacresol; • Personal or immediate family history of medullary thyroid cancer (MTC) or genetic condition that predisposes to MTC (eg, multiple endocrine neoplasia type 2 syndromes); • History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy was already performed), chronic pancreatitis, pancreatitis during a previous treatment with incretin therapies, pancreatectomy; • Body Mass Index (BMI) ≤20 or >40 kg/m².
<p>Main selection criteria for the extension period</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients treated with FRC during the 26-week randomized treatment period. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Patients in the FRC arm receiving rescue therapy and HbA1c >8% at Week 22; • Patients in the FRC arm who discontinued prematurely from FRC treatment before Week 26; • Patients in the GLP-1RA treatment arm after randomization.
<p>Total expected number of patients</p>	<p>Approximately 500 patients randomized in the study (250 patients per group) during the open-label randomized treatment period.</p> <p>Approximately 230 patients are estimated to enter the single-arm extension period with the treatment of FRC.</p>

STUDY TREATMENT(s)	
<p data-bbox="212 297 679 331">Investigational medicinal product(s)</p> <p data-bbox="212 365 376 398">Formulation:</p>	<p data-bbox="695 297 823 331">Test drug</p> <p data-bbox="695 342 1474 443">Insulin glargine/lixisenatide fixed ratio combination (FRC): FRC is supplied as a sterile aqueous solution in a pre-filled disposable SoloStar® pen-injector (100 U/mL insulin glargine with 33 or 50 µg/mL lixisenatide depending on the pen).</p> <p data-bbox="695 454 962 488">Pen-injector devices</p> <p data-bbox="695 499 1449 566">The combination product will be self-administered with a pre-filled disposable SoloStar® pen-injector.</p> <p data-bbox="695 577 1474 768">The dose of the combination is titrated according to the patient's need for insulin. Note that only the dose of insulin glargine appears in the pen dosing window. The dose (µg) of lixisenatide does not appear in the dose window even though lixisenatide is pre-mixed in the cartridge. The lixisenatide dose is increased or decreased along with insulin glargine dose changes and also depends on which Pen (peach or olive) is used.</p> <p data-bbox="695 779 1465 869">There are two pens (peach and olive) with different insulin glargine/lixisenatide fixed ratios which allow insulin glargine titration from 10 to 60 U while limiting lixisenatide dose to a maximum of 20 µg/day:</p> <p data-bbox="695 880 1474 1070">Peach Pen: pre-filled disposable SoloStar® pen-injector containing 3 mL of sterile solution of 100 U/mL insulin glargine and 50 µg/mL lixisenatide in ratio of 2:1 (2 units of insulin glargine per 1 µg lixisenatide), glycerol [REDACTED], methionine, meta-cresol, zinc [REDACTED], HCl/NaOH and water for injection. This pen allows administration of daily combination doses between 10 U/5 µg and 40 U/20 µg; The Peach Pen will be the pen used for starting the combination treatment.</p> <p data-bbox="695 1081 1474 1238">Olive Pen: pre-filled disposable SoloStar® pen-injector containing 3 mL of sterile solution of 100 U/mL insulin glargine and 33 µg/mL lixisenatide in ratio of 3:1 (3 units of insulin glargine per 1 µg lixisenatide), glycerol [REDACTED], methionine, meta-cresol, zinc [REDACTED], HCl/NaOH and water for injection. This pen allows administration of daily combination doses between 30 U/10 µg and 60 U/20 µg.</p> <p data-bbox="695 1249 879 1283">Control drugs</p> <p data-bbox="695 1294 1474 1485">Liraglutide (Victoza®)* is supplied as a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg. Each pen is pre-filled with 3 mL of a clear colorless solution containing 6 mg/mL of liraglutide (free-base, anhydrous) and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection.</p> <p data-bbox="695 1496 1474 1742">Exenatide (Byetta®)* is supplied for subcutaneous (SC) injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen-injector (prefilled pen). Each milliliter (mL) contains 250 micrograms (µg) synthetic exenatide, metacresol, mannitol, and glacial acetic acid and sodium acetate trihydrate in water for injection. Two prefilled pens are available to deliver unit doses of 5 µg (1.2 mL prefilled pen) or 10 µg (2.4 mL prefilled pen). Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).</p> <p data-bbox="695 1753 1474 1944">Exenatide extended-release (Bydureon®)* is supplied as a sterile powder (already diluted in pens) and administered by subcutaneous injection. A prefilled pen contains 2mg exenatide, polylactide-co-glycolide, sucrose, carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, water for injection (sodium hydroxide may be added during manufacture of pens for</p>

	<p>ph adjustment). Each pen is a single dose of 2 mg to be injected once a week.</p> <p>Albiglutide (Tanzeum®)* is supplied as a sterile powder diluted in pens and administered by subcutaneous injection.</p> <p>30-mg Pen for injection (for subcutaneous use) contains 40.3 mg lyophilized albiglutide and 0.65 mL Water for Injection diluent designed to deliver a dose of 30 mg in a volume of 0.5 mL after reconstitution.</p> <p>50-mg Pen for injection (for subcutaneous use) contains 67 mg lyophilized albiglutide and 0.65 mL Water for Injection diluent designed to deliver a dose of 50 mg in a volume of 0.5 mL after reconstitution.</p> <p>Inactive ingredients include 153 mM mannitol, 0.01% (w/w) polysorbate 80, 10 mM sodium phosphate, and 117 mM trehalose dihydrate.</p> <p>Each pen is a single dose of 30mg or 50mg to be injected once a week.</p> <p>Dulaglutide (Trulicity®)* is supplied as a sterile solution in pens or syringes and administered by subcutaneous injection</p> <p>Each single dose pen contains 0.75 mg dulaglutide/0.5 mL solution or 1.5 mg dulaglutide/0.5 mL solution with following excipients: citric acid anhydrous (0.07 mg), mannitol (23.2 mg), polysorbate 80 (0.10 mg), trisodium citrate dihydrate (1.37 mg), water for injection.</p> <p>Each pen is a single dose of 0.75mg or 1.5mg to be injected once a week.</p> <p>*If available at country level</p>
<p>Route(s) of administration:</p>	<p>Subcutaneous for Investigational medicinal product (IMP)</p>
<p>Dose regimen:</p>	<p>Insulin glargine/lixisenatide fixed ratio combination (FRC)</p> <p>Injection time</p> <p>FRC: should be self-administered once daily in the morning in the hour (0 to 60 minutes) before breakfast.</p> <p>Starting dose</p> <p>FRC: treatment will be initiated with the Peach Pen. The initial daily dose of FRC to be administered will be 10 U: this corresponds to an initial associated dose of 10 U of insulin glargine and lixisenatide of 5 µg according to the 2 U/1 µg fixed ratio used in the Peach Pen.</p> <p>Dose adjustment</p> <p>During the first 8 weeks of treatment, from V3 (Week 0) to V19 (Week 8), the dose will be titrated twice a week as far as possible (see below algorithm in Table 1.) based on the insulin glargine dose, until the patient reaches a target fasting SMPG of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. Titration will be done at the scheduled weekly visits (V5, V7, V9, V11, V13, V15, V17, V19) plus at one additional weekly titration phone call visit to be scheduled between the weekly visits (V4, V6, V8, V10, V12, V14, V16, V18). The additional titration phone call visit should be scheduled to allow for at least two days in between successive visits (example: weekly visits to occur on Mondays and titration phone calls to occur on Thursdays or Fridays). In case the additional phone call is missed during the week, the titration should continue as per the originally planned schedule. Thereafter from V19 (Week 8) until V28 (Week 26), the dose will be adjusted as necessary to maintain this fasting SMPG target, with recommendation to evaluate the dose at least once a week. Twice a week titration can be continued</p>

	<p>if deemed appropriate by the investigator.</p> <p>Dose changes are based on the lowest fasting SMPG value from the last 3 measurements, which may include the value measured on the day of titration, measured by the patient using glucometers and accessories supplied by the sponsor. However, sound clinical judgment is to be exercised during titration and investigators may decide to further titrate if the lowest value from the last 3 measurements is between 80 and 100 mg/dL but the two other values are well above 100 mg/dL, if they believe that is an appropriate intervention in the best interest of the patient.</p> <p>Investigators may adjust or stop titration, or temporarily reduce dose if they believe further titration would be hazardous at that time-</p> <p>The total daily dose will be capped at 60 U. In case a dose >60 U is needed to maintain glucose parameters below the threshold value defined for rescue therapy, the dose should be kept at 60 U and a rescue therapy should be introduced (see section on rescue therapy).</p> <p>Patients continuing in the extension period will continue with their same dose and dose adjustment algorithm as during the randomized treatment period.</p> <p style="text-align: center;">Table 1 - Dose adjustment algorithm for Insulin glargine/ lixisenatide fixed ratio combination</p> <table border="1" style="width: 100%;"> <thead> <tr> <th style="text-align: center;">The lowest fasting SMPG value from the last 3 measurements, which may include the value measured on the day of titration</th> <th style="text-align: center;">FRC dose adjustments (U/day)</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">>140 mg/dL (>7.8 mmol/L)</td> <td style="text-align: center;">+4</td> </tr> <tr> <td style="text-align: center;">>100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L)</td> <td style="text-align: center;">+2</td> </tr> <tr> <td style="text-align: center;">Glycemic target: 80 to 100 mg/dL (4.4 and 5.6 mmol/L), inclusive</td> <td style="text-align: center;">No change</td> </tr> <tr> <td style="text-align: center;">≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)</td> <td style="text-align: center;">-2</td> </tr> <tr> <td style="text-align: center;"><60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week.</td> <td style="text-align: center;">-2 to -4 or at the discretion of the Investigator or designee</td> </tr> </tbody> </table> <p>Choice of Peach Pen or Olive Pen</p> <ul style="list-style-type: none"> • If the patient needs a FRC dose of 10 to 40 U, use the Peach Pen (insulin glargine/lixisenatide 2:1). • If the patient needs a FRC dose of 41 to 60 U, use the Olive Pen only (insulin glargine/lixisenatide 3:1). • Daily doses of FRC higher than 60 U must not be administrated. <p>Liraglutide (Victoza®) or Exenatide (Byetta®) or Exenatide extended-release (Bydureon®) or Albiglutide (Tanzeum®) or Dulaglutide (Trulicity®)</p> <p>Injection time</p> <p>Victoza® can be administered once daily at any time of day, independently of meals.</p> <p>Byetta® can be administrated twice daily at any time within the 60 minute period before the morning and evening meal (or two main meals of the day,</p>	The lowest fasting SMPG value from the last 3 measurements, which may include the value measured on the day of titration	FRC dose adjustments (U/day)	>140 mg/dL (>7.8 mmol/L)	+4	>100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L)	+2	Glycemic target: 80 to 100 mg/dL (4.4 and 5.6 mmol/L), inclusive	No change	≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	-2	<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week.	-2 to -4 or at the discretion of the Investigator or designee
The lowest fasting SMPG value from the last 3 measurements, which may include the value measured on the day of titration	FRC dose adjustments (U/day)												
>140 mg/dL (>7.8 mmol/L)	+4												
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<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week.	-2 to -4 or at the discretion of the Investigator or designee												

	<p>approximately 6 hours or more apart). Byetta® should not be administered after a meal.</p> <p>Bydureon®, Tanzeum®, Trulicity® can be administered once a week at any time of day, independently of meals.</p> <p>Dosing</p> <p>Patients randomized to the GLP-1 receptor agonist group will continue the same daily dose and regimen of GLP-1 receptor agonist as prior to randomization.</p>
<p>Noninvestigational medicinal product(s)</p> <p>Background therapy</p>	<p>Background therapy: (commercial metformin tablet ± pioglitazone tablet ± SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)) and rescue therapy will be considered as non-investigational medicinal products (NIMP(s)).</p> <p>Metformin and pioglitazone (if applicable) and SGLT2 inhibitors (if applicable) should be administered according to local product labeling.</p> <p>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 visit (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).</p> <p>The doses of metformin and pioglitazone (if applicable) and SGLT2 inhibitors (if applicable) should be continued and should remain stable throughout the study unless there is a specific safety issue related to this treatment.</p>
<p>Noninvestigational medicinal product(s)</p> <p>Rescue therapy:</p>	<p>In case HbA1c is above 8% at Week 12 or later on, the Investigator will receive an alert issued by the central laboratory and should ensure that no reasonable explanation exists for insufficient glucose control and in particular that there is no intercurrent disease which may jeopardize glycemic control (eg, infectious disease), that the treatments are given at the planned dose and compliance to treatment and diet and lifestyle is appropriate. HbA1c assessment should be scheduled at next visit (if next visit is a phone call, it should be replaced by an unscheduled visit at site) or within 4 weeks. If appropriate corrective action fails and if the repeated HbA1c remains above 8%, a rescue therapy should be considered according to the Investigator's judgment.</p> <p>For patients in the FRC arm(s):</p> <ul style="list-style-type: none"> • rescue therapy is recommended only if further dose titration is not possible, ie, 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 as rescue therapy in the FRC arm. <p>For patients in the GLP-1 RA arm:</p> <ul style="list-style-type: none"> • suggested rescue therapy is basal insulin at the investigator's discretion. <p>During the extension period, suggested rescue therapy is rapid acting insulin (insulin-glulisine when available) for all patients.</p> <p>If the rescue therapy is initiated during the randomized treatment period all assessments planned at the end of randomized treatment visit (V28) are to be performed before initiating rescue therapy. If the rescue therapy is initiated during the extension period all assessments planned at the end of extension treatment visit (V35) are to be performed before initiating the rescue therapy. After these assessments are completed and rescue therapy initiated, the patient will remain in the study and continue to administer the study treatment (including</p>

	<p>background therapy). The planned visits and assessments should be performed until the last scheduled visit.</p> <p>If the patient is eligible for the extension period with rescue therapy initiated during the randomized treatment period, the rescue therapy may continue in the extension period, as required.</p>
<p>ENDPOINT(S)</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • Change in HbA1c from baseline to Week 26. <p>Secondary endpoint(s):</p> <p>Efficacy</p> <ul style="list-style-type: none"> • Percentage of patients reaching HbA1c <7 % (53 mmol/mol) or ≤6.5% (48 mmol/mol) at Week 26; • 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; • Percentage of patients requiring rescue therapy during the 26 week treatment period; • Change in body weight from baseline to Week 26. <p>Other endpoints:</p> <ul style="list-style-type: none"> • Insulin glargine and lixisenatide doses at Week 26 in the combination group; • C-peptide evaluation during standardized meal test from baseline to Week 26; • Percentage of patients reaching HbA1c <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. <p>Safety endpoints:</p> <ul style="list-style-type: none"> • Symptomatic hypoglycemia (documented, probable, severe symptomatic hypoglycemia); • Adverse events (AE), serious adverse events (SAE), adverse event of special interest (AESI), AEs requiring specific monitoring and reporting on specific electronic case report forms (e-CRFs) (suspected allergic reactions, patients with increased pancreatic enzymes >2 ULN/pancreatic events, patients with increased calcitonin ≥20 pg/mL, Device-related events (DRE)); • Safety laboratory values; • Vital signs; • Electrocardiogram (ECG); • Immunogenicity (antibody variables, FRC group): anti-insulin and anti-

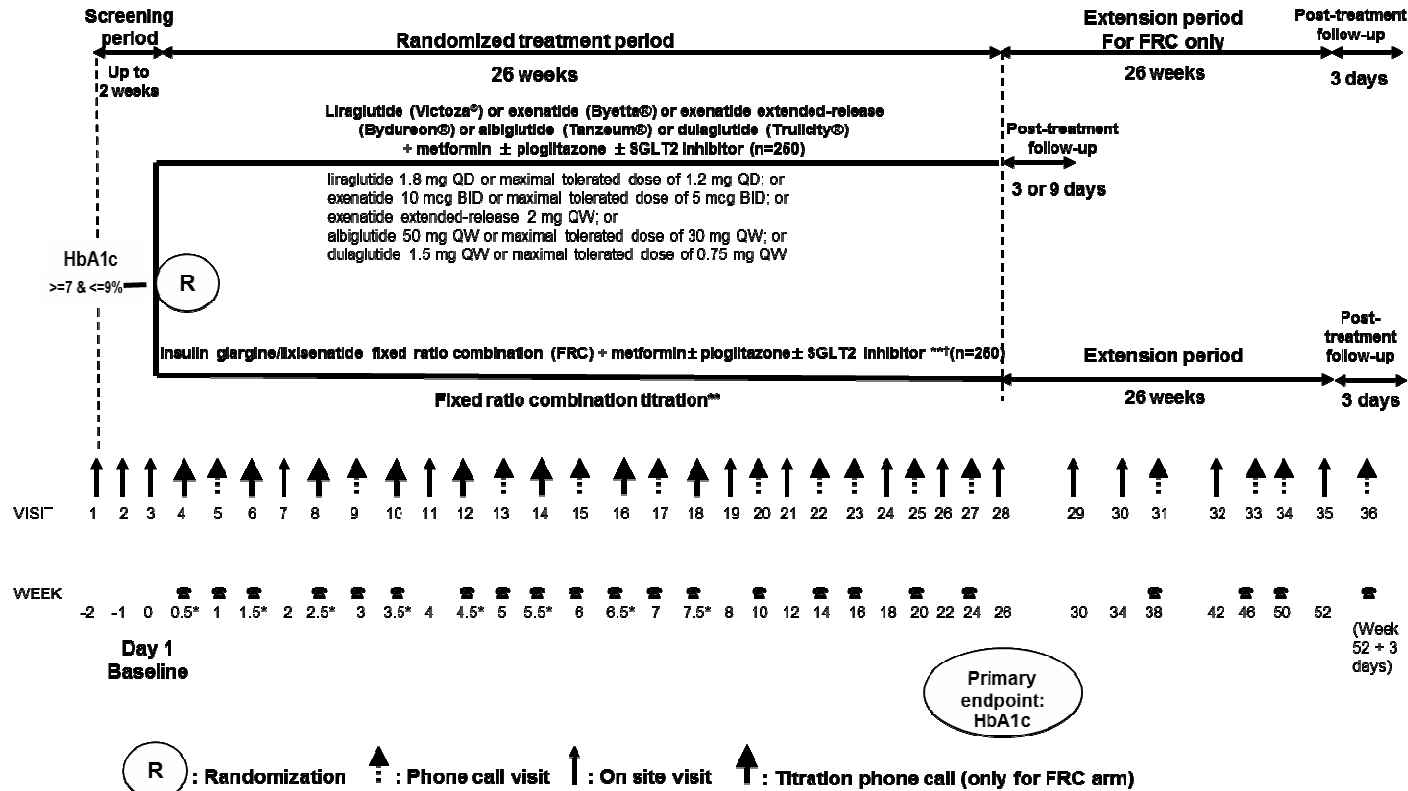
	<p>lixisenatide antibodies.</p> <p>Endpoints of the extension period</p> <p>All primary and secondary efficacy, safety, PK and other endpoints will be also assessed at the end of the extension period (Week 52).</p>
<p>ASSESSMENT SCHEDULE</p>	<p>Visit schedule</p> <p>The schedule of study-related procedures/assessments is detailed in the Study Flowchart (Section 1.2).</p> <p>Early termination</p> <p>Patients who prematurely and permanently discontinue IMP administration during the randomized treatment period or during the extension period for any reason should have a visit as soon as possible with the assessments normally planned for the last dosing day with the IMP, ie, the "final on-treatment assessment". Afterward, these patients should continue in the study up to the scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol (except for the safety post-treatment follow-up).</p>
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination:</p> <p>A sample size of 250 patients per group will provide 90% power to detect a difference of 0.4% in the HbA1c change from baseline to Week 26 between the FRC and GLP-1 receptor agonist arm. This calculation assumes a common standard deviation of 1.1% at the 5% significance level (2-sided) and a common drop-out rate of 20% at 26 weeks. It is based on the intent-To-Treat (ITT) analysis and also assumes in the conservative manner that the FRC dropped patients will respond as the control patients, ie, no treatment difference between FRC dropped patients and the control patients.</p> <p>Analysis population:</p> <p>The primary efficacy population will be the modified Intent-To-Treat (mITT) population, which includes all randomized patients who have a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy endpoints, irrespective of compliance with the study protocol and procedures. Patients will be analyzed in efficacy analyses by the treatment regimen allocated by interactive response technology (IRT) according to the randomization schedule at randomization visit (as randomized).</p> <p>The safety analysis will be conducted on the safety population, defined as all randomized patients exposed to at least one dose of investigational medicinal product, regardless of the amount of treatment administered. Patients will be analyzed according to the treatment regimen actually received.</p> <p>Primary efficacy endpoint analysis:</p> <p>Analyses of the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) will be performed using the mITT population, using HbA1c values obtained from the scheduled visits during the 26-week randomized treatment period, including those obtained after IMP discontinuation or rescue medication use.</p> <p>The statistical test will be two-sided at the alpha level of 0.05.</p> <p>The primary analysis method for the primary efficacy endpoint will be a mixed-effect model with repeated measures (MMRM) under the missing at random framework. The MMRM model will include the treatment groups, randomization</p>

	<p>strata of screening (V 1) HbA1c (<8%, ≥8%), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening visit, treatment-by-visit interaction, and world region as fixed-effect factors, and the baseline HbA1c-by-visit interaction as covariate. The baseline value is defined as the last available value prior to the first dose administration of investigational medicinal product or the last available value on or before the date of randomization if not treated with open-label IMP. The adjusted mean change in HbA1c 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 and the 95% confidence interval (CI) for the adjusted mean.</p> <p>The MMRM model will be run using Statistical Analysis System (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 HbA1c measurements.</p> <p>For the primary efficacy endpoint, sensitivity analyses will be performed as necessary to explore different methods for handling missing data.</p> <p>Secondary efficacy endpoint analysis:</p> <p>The continuous secondary efficacy endpoints will be analyzed using a similar MMRM method. Differences between treatment groups and CI will be estimated within the framework of MMRM. Categorical efficacy endpoints will be analyzed by Cochran Mantel Haenszel method stratified by the randomization strata.</p> <p>Other endpoint analysis:</p> <p>Descriptive statistics will be summarized by treatment group. For PK parameters, lixisenatide total plasma concentrations 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.</p> <p>Descriptive statistics will also be summarized for efficacy endpoints at scheduled visit for FRC group for the whole study period including the extension period.</p> <p>Safety analysis:</p> <p>Safety analyses will be descriptive, based on the safety population (randomized and exposed). They will be performed for the 26 week randomized treatment period and for the whole study period including the extension period (for FRC group only) as appropriate.</p> <p>Treatment-emergent adverse events (TEAEs) are defined as AEs that developed or worsened 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-RA) after the last administration.</p>
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<p>DURATION OF STUDY PERIOD (per patient)</p>	<p>Maximum duration for FRC patients of approximately 55 weeks: an up to 2-week screening period, a 26-week randomized treatment period, a 26-week extension period and a 3-day post-treatment safety follow-up period.</p> <p>Maximum duration for GLP1-RA patients of approximately 29 weeks: an up to 2-week screening period, a 26-week randomized treatment period, and a 3 or 9-day post-treatment safety follow-up period.</p>
<p>STUDY COMMITTEES</p>	<p>Steering Committee: <input checked="" type="checkbox"/> Yes</p> <p>The Steering Committee is composed of scientists with clinical and methodological expertise in diabetes and conduct of clinical trials. This Committee, led by a Chairman, is responsible for producing and conducting a scientifically sound study and for ensuring accurate reporting of the study. In that capacity, the Steering Committee must address scientific issues encountered during the study.</p> <p>Allergic Reaction Assessment Committee (ARAC): <input checked="" type="checkbox"/> Yes</p> <p>The ARAC is a committee of experts in the field of allergy, independent from the Sponsor and the Investigators that will assess all allergic or allergic-like reactions occurring during the study. The ARAC reviews the cases in a blinded manner with regard to study treatment.</p> <p>Pancreatic Safety Assessment Committee (PSAC): <input checked="" type="checkbox"/> Yes</p> <p>The PSAC is a committee of experts in the field of pancreatitis and pancreatic neoplasm, independent from the Sponsor and the Investigators, implemented to assess pancreatic events that may occur during the study. The PSAC will review selected pancreatic events, including pancreatitis, pancreatic neoplasms and abnormal levels of amylase or lipase. This review will be conducted in a blinded manner with regard to study treatment.</p>

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* 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 10U 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 (4.4-5.8 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.

1.2 STUDY FLOW CHART

	Screening period		Randomized treatment period ^b																									Post-treatment follow-up ^c			
VISIT ^a	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 ^d	follow-up		
WEEK	-2	-1	0	0.5 ^e	1	1.5 ^e	2	2.5 ^e	3	3.5 ^e	4	4.5 ^e	5	5.5 ^e	6	6.5 ^e	7	7.5 ^e	8	10	12	14	16	18	20	22	24	26			
Informed Consent	X																														
Inclusion/Exclusion Criteria	X		X																												
Medical, surgical, and diabetes histories, alcohol & smoking habits, demography, prior medications	X																														
Physical Examination	X																												X		
Height	X																														
Body weight	X		X								X									X		X				X			X		
Vital Signs (heart rate, blood pressure)	X	X	X				X				X								X		X				X				X		
12-lead ECG	X																												X		
Diet and Lifestyle counseling			X (once at V2 or 3)																			X							X		
IRT contact	X		X				X				X								X		X				X		X		X	X	
Randomization			X																												
Concomitant medication recording	Continuously assessed and recorded all along the study																														
AE/SAE/Symptomatic Hypoglycemia ^f	Continuously assessed and recorded all along the study																														
Glucometer dispensation & training (including training on glucose measurements) ^g		X																													
Diary dispensation / collection (reviewed at each on-site visit)		X	X				X				X								X		X				X		X		X		

VISIT ^a	Screening period		Randomized treatment period ^b																									Post-treatment follow-up ^c			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 ^d	follow-up		
WEEK	-2	-1	0	0.5 ^e	1	1.5 ^e	2	2.5 ^e	3	3.5 ^e	4	4.5 ^e	5	5.5 ^e	6	6.5 ^e	7	7.5 ^e	8	10	12	14	16	18	20	22	24	26			
Pen-injector and self-injection training ^g			X																												
Fasting SMPG measured every day before breakfast			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X												
Fasting SMPG measured at least three times per week before breakfast																				X	X	X	X	X	X	X	X	X	X		
Titration phone calls (FRC arm only) ^e				X		X		X		X		X		X		X		X													
7-point SMPG profiles (on 2 different days in the week prior to the visit) ^h			X																		X								X		
IMPs dispensation ⁱ			X				X				X								X		X			X		X					
Recording of GLP-1 receptor agonist daily/weekly dose (mg or µg) (control arm)	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		
Recording of FRC dose (U)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Count returned pens							X				X								X		X			X		X		X			
Compliance check			X				X				X								X		X			X		X		X			
Central laboratory testing																															
HbA1c	X		X																X		X			X		X		X			
Fasting Plasma Glucose	X	X ^j	X								X								X		X					X		X ^j			
2-h standardized meal test ⁱ		X																											X		
Total-, LDL-, HDL-Cholesterol, triglycerides ^k			X																										X		
Urinalysis ^l	X	X																													
Hepatitis B surface antigen and hepatitis C antibody	X																														

VISIT ^a	Screening period		Randomized treatment period ^b																									Post-treatment follow-up ^c		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 ^d	follow-up	
WEEK	-2	-1	0	0.5 ^e	1	1.5 ^e	2	2.5 ^e	3	3.5 ^e	4	4.5 ^e	5	5.5 ^e	6	6.5 ^e	7	7.5 ^e	8	10	12	14	16	18	20	22	24	26		
Women only: FSH (if necessary to define menopausal status) ^m	X																													
Women only: serum pregnancy test (if childbearing potential)	X		X																		X								X	
Safety laboratory ⁿ hematology, serum chemistry	X		X																		X								X	
Amylase, Lipase	X		X				X				X										X								X	
Serum Calcitonin	X		X																		X								X	
Anti-lixisenatide and anti-insulin antibodies (only in FRC group) ^o			X								X ^q										X ^q							X ^r		
Total plasma lixisenatide concentration (only in FRC group) ^p			X								X										X							X		

VISIT ^a	Extension period								Post-treatment follow-up
	28a	29	30	31	32	33	34	35	follow-up ^c
WEEK	26	30	34	38	42	46	50	52	
Inclusion/Exclusion Criteria	X								
Physical Examination	X							X	
Body weight	X		X		X			X	
Vital Signs (heart rate, blood pressure)	X		X		X			X	
12-lead ECG	X							X	
Diet and Lifestyle counseling	X				X				
IRT contact	X		X		X			X	X
Concomitant medication recording	Continuously assessed and recorded all along the study								
AE/SAE/Symptomatic Hypoglycemia ^f	Continuously assessed and recorded all along the study								
Diary dispensation / collection (reviewed at each on-site visit)	X		X		X			X	
Fasting SMPG measured at least three times per week before breakfast	X	X	X	X	X	X	X	X	
7-point SMPG profiles (on 2 different days in the week prior to the visit) ^h	X							X	
IMPs dispensation ⁱ	X		X		X				
Recording of FRC dose (U)	X	X	X	X	X	X	X	X	
Count returned pens	X		X		X			X	
Compliance check	X		X		X			X	
Central laboratory testing									
HbA1c	X		X		X			X	
Fasting Plasma Glucose	X		X		X			X ^j	
2-h standardized meal test ^j	X							X	
Total-; LDL; HDL-Cholesterol, triglycerides ^k	X							X	
Women only: serum pregnancy test (if childbearing potential)	X		X		X			X	

VISIT ^a	Extension period								Post-treatment follow-up
	28a	29	30	31	32	33	34	35	follow-up ^c
WEEK	26	30	34	38	42	46	50	52	
Safety laboratory ⁿ hematology, serum chemistry	X							X	
Amylase, lipase	X		X		X			X	
Serum calcitonin	X		X		X			X	
Anti-lixisenatide and anti-insulin antibodies ^o	X							X ^r	
Total plasma lixisenatide concentration ^p	X							X	

- a During the screening period and for randomization visit a visit window of ± 3 days is acceptable, taking V1 as reference until the randomization visit (V3). During the treatment period a visit window of ± 3 days is acceptable taking V3 as reference for V5 to V19 (except for additional titration calls for fixed ratio combination treatment arms; please refer to footnote e), and a visit window of ± 5 days is acceptable from V20 to V35. A visit window of -1 day or + 3 days for the post-treatment follow-up visit is acceptable using the day of V28 and V35 respectively as reference. For patients receiving weekly GLP1-RA, the post-treatment follow-up visit is scheduled 9 days after V28 with the same visit window as for the other patients. If one visit date is changed, the next visit should take place according to the original schedule.
- b Additional phone calls for titration purposes should be scheduled as often as deemed necessary by the Investigator.
- c Post-treatment follow-up visit: This visit can be a phone call visit, or an on-site visit in case of ongoing or new adverse event during the post-treatment period, if necessary.
- d **In case of premature permanent IMP discontinuation**, patients should have a visit as soon as possible with the assessments normally planned in V28 or V35 for randomized treatment or extension period, respectively (the 2-hour standardized meal test is performed only if the patient receives the IMP on the day of the meal test). Afterwards, the patients should continue in the study up to the scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol (except for the 3 day safety post-treatment follow-up). **In case of rescue therapy**, all assessments planned in V28 or V35 for randomized treatment or extension period, respectively should be performed before starting rescue therapy, patients then continue the study treatment (including metformin \pm pioglitazone \pm SGLT2 inhibitor), and all visits and assessments should be performed as scheduled.
- e These additional titration phone calls are necessary only in the fixed ratio combination (FRC) arms during the first 8 weeks of treatment, from V3 (Week 0) to V19 (Week 8), hereafter, from V19 (Week 8) until V28 (Week 26), the dose will be adjusted as necessary to maintain this fasting SMPG target, with recommendation to evaluate the dose at least once a week. Please see [Section 8.1.4.1](#) on dose adjustment.
- f Whenever the patient feels hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation.
- g The training can be repeated as often as necessary.
- h The 7-point SMPG profile should be measured at the following 7 points: pre-prandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime.
- i Any patient treated with a **once weekly GLP-1 RA** upon entering the study who is assigned to receive FRC treatment should not receive their first dose until at least 1 week after their last dose of GLP-1 RA. For these patients baseline visit must be scheduled at least 1 week after administering their last dose of GLP1.
- j At V2 and V28 and V35, FPG and C-peptide are part of the standardized meal test. The standardized meal contains approximately 600 kcal and is composed of 50 to 55% carbohydrate, 15 to 20% protein and 25 to 30% fat. The standardized meal for all patients should be consumed within a 15-minute period.
- k LDL = low density lipoprotein, HDL = high density lipoprotein.
- l Screening urinalysis at V1: (pH, glucose, ketones, leucocytes, blood/hemoglobin, protein), Urinalysis at V2 (Albumin/creatinine ratio (1st morning urines)

- m* FSH = follicle stimulating hormone.
- n* Safety Laboratory: hematology = White blood cell count (WBC), Red blood cell count (RBC), Hemoglobin, Hematocrit, platelets, differential blood count (Neutrophils, lymphocytes, monocytes, eosinophils, basophils). Serum chemistry = total bilirubin, AST, ALT, alkaline phosphatase (ALP), creatinine, uric acid, sodium, potassium, phosphorus, calcium.
- o* Samples for antibody assessment to be taken prior to IMP injection.
- p* Total plasma concentrations of lixisenatide for patients on FRC will be assessed in the time frame from 1 to 4 hours post-injection at Day 1 of the treatment and prior to injection as well as in the time frame from 1 to 4 hours post-injection at other visits. Samples will also be taken in case of premature discontinuation from IMP or in case of rescue therapy initiation, if possible. In case of premature discontinuation, one PK sample is sufficient if the last dose of IMP is not administered at the visit.
- q* At V11 and V21, only samples for anti-lixisenatide antibody assessment.
- r* One additional sample for potential additional assessments of immunogenicity will be taken at Week 26 (if the patient completes the study after Week 26) or Week 52 (if the patient participates in the extension period) or in case of premature discontinuation.

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3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ARAC:	allergic reaction assessment committee
AST:	aspartate aminotransferase
ATC:	anatomic or therapeutic category
BID:	bis in die = twice daily
BMI:	body mass index
CI:	confidence interval
CSR:	clinical study report
DRE:	device-related event
DREQ:	device-related event questionnaire
EASD:	European Association for the Study of Diabetes
ECG:	electrocardiogram
e-CRF:	electronic case report form
FPG:	fasting plasma glucose
FRC:	fixed Ratio Combination
GCP:	good clinical practice
GFR:	glomerular filtration rate
GLP-1 RA:	glucagon-like peptide-1 receptor agonist
HbA1c:	hemoglobin A1c
HDL:	high density lipoprotein
HLGT:	high level group term
HLT:	high level term
ICH:	International Council for Harmonization
IEC:	independent ethics committee
IgM:	immunoglobulin M
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
LDL:	low density lipoprotein
mITT:	modified intent-to-treat
MMRM:	mixed-effect model with repeated measures
MTC:	medullary thyroid cancer
MTD:	maximum tolerated dose
NIMP:	noninvestigational medicinal product
PCSA:	potentially clinically significant abnormality
PI:	prescribing information

PPG:	post-prandial plasma glucose
PSAC:	pancreatic safety assessment committee
PT:	preferred term
PTC:	product technical complaint
QD:	quaque die = once daily
QW:	once weekly
SAE:	serious adverse event
SAS:	statistical analysis system
SC:	subcutaneous
SD:	standard deviation
SmPC:	summary of product characteristics
SMPG:	self-monitored plasma glucose
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal range
WHO-DD:	World Health Organization - Drug Dictionary

4 INTRODUCTION AND RATIONALE

Study LixiLan-G (EFC13794) will evaluate the efficacy and safety of the combination of basal insulin glargine (Lantus®) and the glucagon-like peptide-1 receptor agonist (GLP-1 RA) lixisenatide in patients with type 2 diabetes mellitus (T2DM) not sufficiently controlled on oral anti-diabetic drug (OAD) therapy and GLP-1 receptor agonist therapy (liraglutide (Victoza®), exenatide (Byetta®), exenatide extended-release (Bydureon®), albiglutide (Tanzeum®), and dulaglutide (Trulicity®).

Lixisenatide (AVE0010, Lyxumia®) is a polypeptide with pronounced glucagon-like peptide 1 (GLP-1) agonist activity, approved since 2013 in the European Union (EU), Japan, Mexico, and other parts of the world for treatment of adults with T2DM to achieve glycemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycemic control. In the US it is approved since 2016 as Adlyxin®. The indication may vary slightly across the countries where lixisenatide is approved. Other information concerning lixisenatide is available in the Clinical Investigator's Brochure (1) and in the Lyxumia® Summary of Product Characteristics (SmPC) (2) and Adlyxin® Prescribing Information (PI) (3).

Insulin glargine (HOE901, Lantus®), an analogue of human insulin, provides 24-hour basal insulin supply after single dose subcutaneous injection. Lantus® has been marketed since June 2000 in Europe and since April 2000 in the USA and other parts of the world. Lantus® is indicated for the treatment of adult and pediatric patients with T1DM or adult patients with T2DM who require basal (long-acting) insulin for the control of hyperglycemia. Other information concerning insulin glargine is available the Lantus® SmPC (4) and Lantus® PI (5).

Since both lixisenatide and insulin glargine are efficacious when given once daily, and have similar physicochemical features such as good solubility at low pH, both components can be mixed as a defined fixed ratio formulation to be delivered in one single injection.

Several GLP-1 receptor agonists (GLP-1 RA) are approved throughout the world. Liraglutide (Victoza®) has been marketed since 2009 in Europe and 2010 in the USA, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The indication may vary slightly across the countries where liraglutide is approved. Detailed information concerning liraglutide is available in the Victoza® SmPC (6) and Victoza® PI (7).

Exenatide (Byetta®) has been initially approved in Europe in 2006 and in 2005 in the USA, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The indication may vary slightly across the countries where Byetta® is approved. Detailed information concerning Byetta® is available in the Byetta® SmPC (8) and Byetta® PI (9). The extended-release version of Exenatide (Bydureon®) has been initially approved in Europe in 2011 and in 2012 in the USA, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The indication may vary slightly across the countries where Bydureon® is approved. Other information concerning Bydureon® is available in the Bydureon® SmPC (10) and Bydureon® PI (11).

Albiglutide has been initially approved in 2014 and marketed under the trade name Tanzeum® in the USA. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The indication may vary slightly across the countries where Tanzeum® is approved. Detailed information concerning albiglutide is available in-Tanzeum® PI (12).

Dulaglutide (Trulicity®) has been initially approved in Europe and in the USA in 2014, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The indication may vary slightly across the countries where Trulicity® is approved. Detailed information concerning Trulicity® is available in the Trulicity® SmPC (13) and Trulicity® PI (14).

Metformin is generally considered to be the most appropriate first-line therapy for treating T2DM, but there is no general agreement on how to advance treatment when metformin and lifestyle modification become insufficient. As additional OAD therapy, thiazolidinediones (TZDs), and in particular pioglitazone, could be used in addition to metformin, among other OAD therapies. Another recently introduced class of OADs, the SGLT2 inhibitors, is steadily becoming a choice early in the stepwise advancing to dual and triple combination therapy. The new class of GLP-1 receptor agonist drugs has become increasingly used by health care professionals and has been included as part of both two and three drug therapeutic regimens in the recent American Diabetes Association/European association of the study of diabetes (ADA/EASD) treatment algorithm (15). However as with most type 2 diabetes drugs, GLP-1 RAs may fail after some time, and considering the progressive nature of T2DM, this means that a significant proportion of patients will eventually require an insulin-based combination therapy to attain and sustain glycemic control.

The combined treatment of a GLP-1 RA with long acting basal insulin has been tested in many studies (16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26). Different study designs have confirmed the original findings of Buse et al. (20) that the association of these two biological entities is advantageous in patients with T2DM (27). In addition to improving glycemic control, the association of the two can maximize other benefits and at the same time minimize some of the limitations of the other. While the studies conducted to date are heterogeneous in design, generally speaking, the combination promises to increase the number of patients at target with minimal weight gain or even weight loss while maintaining a manageable hypoglycemia profile. Therefore, the combination of basal insulin with a GLP-1 receptor agonist may provide an improved benefit/risk profile compared with each used individually.

As basal insulin products target primarily, although not exclusively, fasting hyperglycemia, and are often given once daily, a desirable combination would be with a GLP-1 receptor agonist such as lixisenatide, which, when given once daily, still effectively acts on post-prandial glycemia due to slowing down gastric emptying even when the ability to restore glucose sensitive insulin secretion is exhausted or limited.

Given all the above, for patients who are not able to control their type 2 diabetes with OAD therapy and a GLP-1 RA, treatment intensification with the insulin glargine/lixisenatide fixed ratio combination (FRC) as a once daily injection by an easy to-use device could represent a valuable option in the management of their disease. The basal insulin Lantus® will provide a predictable and timely effect in reducing glycosylated hemoglobin A_{1c} (HbA_{1c}), and the GLP-1

receptor agonist lixisenatide will have additional effect on glycemic control while mitigating body weight gain and hypoglycemia that can occur with insulin intensification.

The safety and efficacy of the FRC has been assessed in 2 phase 3 studies:

- Study EFC12404 (LixiLan-O): A randomized, 30-week, active-controlled, open-label, 3 treatment arm, parallel-group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide FRC to insulin glargine alone and to Lixisenatide alone on top of metformin in 1170 patients with T2DM not sufficiently controlled on metformin with or without a second oral antidiabetic drug (OAD). The study met its primary objective demonstrating statistically superior reduction in HbA1c of the FRC compared with lixisenatide and compared with insulin glargine 100 units/mL.

Greater reductions in HbA1c from baseline (8.1%) were achieved with the FRC compared with insulin glargine and lixisenatide (−1.6%, −1.3%, −0.9%, respectively), reaching mean final HbA1c levels of 6.5% for the FRC, versus 6.8% and 7.3% for insulin glargine and lixisenatide, respectively (both $p < 0.0001$). The FRC allowed more patients to reach HbA1c target $< 7\%$ (74% versus 59% for insulin glargine and 33% for lixisenatide; $p < 0.0001$ for all comparison) while preventing the body weight gain usually observed at initiation of an insulin-based therapy, without increasing the hypoglycemia rate compared to insulin glargine alone. The safety profile of the FRC generally reflected those of its components. Compared to lixisenatide, the FRC had markedly lower rates of nausea and vomiting, leading to fewer permanent treatment discontinuations.

- Study EFC12405 (LixiLan-L): A randomized, 30-week, active-controlled, open-label, 2 treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide FRC to insulin glargine with or without metformin, in 736 patients with T2DM not sufficiently controlled on basal insulin. The study met its primary objective demonstrating statistically superior reduction in HbA1c of the FRC compared with insulin glargine 100 units/mL, leading to a value of 6.9% at Week 30 compared to 7.5% with insulin glargine. It allowed more patients to reach HbA1c target $< 7\%$ (55% versus 30% for insulin glargine while preventing or minimizing the body weight gain usually observed at intensification of an insulin-based therapy with no additional risk of hypoglycemia as compared to insulin glargine. Overall, the FRC had a safety profile reflecting those of its components.

The lixisenatide stand-alone product has been developed and approved at a fixed dose of 20 µg once daily (QD) in several countries. The dosing of lixisenatide in the FRC ranges from between 5 to 20 µg.

In the two phase 3 studies as well as in the LixiLan-G (EFC13794) phase 3b study, the combination of insulin glargine and lixisenatide is provided in two fixed ratio solutions delivered by prefilled disposable pen injectors. The dose of the combination is to be titrated according to the insulin needs of the patient. These 2 fixed ratios of the components are intended to obtain a good pharmacological effect within established tolerability limits. The lower end of the dosing range of lixisenatide is defined by the minimum dose for efficacy, the upper end by available safety database. Data derived from studies in T2DM patients and healthy subjects demonstrate that doses of 5-10 µg lixisenatide could provide sufficient concentrations to stimulate glucose sensitive

insulin release and have demonstrated efficacy on HbA1c, while doses of 10 µg have also demonstrated a potent effect on inhibition of gastric emptying (1). It is expected that the majority of the target patient population for the FRC would require 10 to 60 U of Lantus (28).

The following two pens with 2 different strengths of the combination will be used in LixiLan-G (EFC13794) study:

- The FRC 10 to 40 pen (Peach Pen) will deliver a dose from 10 U insulin glargine/5 µg lixisenatide to 40 U insulin glargine/20 µg lixisenatide (2 [units] to 1 [µg] ratio). Each unit of the FRC 10 to 40 pen contains 1 unit of insulin glargine and 0.5 µg of lixisenatide;
- The FRC 30 to 60 pen (Olive Pen) will deliver a dose from 30 U insulin glargine/10 µg lixisenatide to 60 U insulin glargine/20 µg lixisenatide (3 [units] to 1 [µg] ratio). Each unit of the FRC 30 to 60 pen contains 1 unit of insulin glargine and 0.33 µg of lixisenatide.

The LixiLan-G (EFC13794) study will consist of a randomized comparative 26-week treatment period followed by a 26-week single arm extension period for patients randomized to the FRC group. The primary objective of the study is to demonstrate the superiority of the FRC to GLP-1 receptor agonist in HbA1c change from baseline to Week 26 in patients with T2DM not sufficiently controlled on GLP-1 receptor agonist and metformin ± pioglitazone± SGLT2 inhibitor treatments.

The secondary objectives of the study are to assess the effects of the FRC versus GLP-1 receptor agonist on percentage of patients reaching HbA1c targets, fasting plasma glucose, 7-point Self-Monitored Plasma Glucose (SMPG) profile, glycemic control during a standardized meal test and body weight. Other parameters will also be assessed: C-peptide during a standardized meal test, composite endpoint of percentage of patients reaching HbA1c target (<7%) with no weight gain, anti- insulin as well as anti-lixisenatide antibodies and total plasma concentration of lixisenatide before and following injection (FRC group).

Screened patients will enter an up to 2-week screening period. Eligible patients whose HbA1c level at screening is ≥ 7 and $\leq 9\%$ will enter a 26-week open label randomized treatment period comparing the FRC to GLP-1 receptor agonist (Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity®). The treatment period duration is considered sufficient to allow an appropriate evaluation of the effect on HbA1c, plasma glucose levels, body weight and other secondary endpoints.

Patients in the FRC group will start their treatment with the Peach Pen at a dose of 10 units which corresponds to an associated dose of 10 U of insulin glargine and 5 µg of lixisenatide. During the first 8 weeks of treatment, the dose will be titrated twice a week as far as possible until the patient reaches a glycemic target of fasting SMPG in the range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia. Thereafter, the dose will be adjusted as necessary to maintain this fasting SMPG target, with recommendation to evaluate the dose at least once a week. Patients needing a daily FRC dose of 41 U or more will switch to the Olive Pen. The maximal daily dose in the FRC treatment groups is 60 U, which corresponds to an associated dose of 60 U of insulin glargine and 20 µg of lixisenatide. Daily doses of FRC higher than 60 must not be administrated.

Patients in GLP-1 receptor agonist group (liraglutide [Victoza®], or exenatide [Byetta®], exenatide extended-release [Bydureon®], albiglutide [Tanzeum®], and dulaglutide [Trulicity®] will continue to receive the same dose they receive at study entry.

The investigational medicinal products (IMPs) should be administered by deep subcutaneous injection, once daily (for details on timing of administration, please see IMPs dose regimen section in the tabular summary) for FRC and Victoza®, twice daily (BID) for Byetta®, or once weekly for Bydureon®, Tanzeum®, or Trulicity®.

At the end of the randomized treatment period (Week 26) patients treated with the FRC will continue to use the FRC during the next 26 weeks of the extension period. Patients treated with the FRC and on rescue therapy during the randomized period and still having their HbA1c >8% at Week 26 will not be invited to participate in the extension period. The 26-week extension period aims to collect safety, immunogenicity, descriptive efficacy and PK data beyond 26 weeks of treatment with the FRC. Indeed, the pivotal studies with the FRC provided data up to 30 weeks of treatment, and with the safety extension for the LixiLan-G study, additional valuable safety and efficacy data over one year in patients treated with the fixed ratio combination will be provided with the FRC.

In the post-marketing experience with GLP-1 receptor agonists, spontaneously reported cases of pancreatitis raised concerns that drugs in this class could cause pancreatitis. Therefore, patients enrolled in this study should be followed for any evidence of suspected pancreatitis, eg, with symptoms and/or signs of acute abdominal distress or abnormal levels of pancreatic enzymes. Serum amylase and lipase concentrations are to be monitored routinely at screening, baseline and periodically during the study treatment period. As this monitoring may be difficult to interpret in patients who already have high values of amylase or lipase, patients with values above 3 times the upper limit of normal range at screening will not be included in the study. Guidance for Investigators on the follow-up of suspected pancreatitis is specified in the protocol. In addition, a Pancreatic Safety Assessment Committee (PSAC) has been established. The PSAC is a committee of experts in the field of pancreatitis and pancreatic neoplasm, independent from the Sponsor and the Investigators, implemented to assess pancreatic events that may occur during the study.

Information from Victoza® (liraglutide) (6, 7), Bydureon® (exenatide-extended release) (10, 11), Tanzeum® (albiglutide) (, 12), and Trulicity® (dulaglutide) (13, 14) pre-clinical carcinogenicity studies has raised the issue of a potential increased risk of thyroid C-cell hyperplasia and neoplasm. Following a request from the health authorities concerning any clinical study longer than 3 months with a GLP-1 receptor agonist, serum calcitonin will be monitored in this study as a marker of thyroid C-cell hyperplasia and neoplasm, with specific monitoring implemented for patients with value ≥ 20 pg/mL (5.9 pmol/L). As this monitoring may be difficult to interpret in patients who already have high values, those with calcitonin values equal to or above 20 pg/mL (5.9 pmol/L) at screening will not be included in the study.

Like any other peptide product, there is a potential for antibody generation when treated with the FRC. Therefore, assessments of the immunogenicity of insulin glargine and lixisenatide will be performed. Antibodies against insulin glargine are well characterized. Therefore, assessment of anti-insulin antibodies is limited to antibody titers and cross-reactivity to human insulin. For lixisenatide, the time course of formation of antibodies and antibody concentrations will be

investigated. Furthermore, cross-reactivity to GLP-1 and glucagon as well as neutralizing effects against lixisenatide, GLP-1 and glucagon will be assessed.

In order to gain information about exposure to lixisenatide, blood samples will be collected to determine lixisenatide concentrations.

Conclusion on the benefit risk assessment in this study

The FRC is the combination of two products with demonstrated glucose-lowering properties and which are approved for the treatment of adult patients with T2DM to improve glycemic control (insulin glargine was approved in 2000 in Europe and since 2001 in the US as well as many other parts of the world, and lixisenatide was approved in 2013 in Europe and other countries).

The type and incidence of adverse events observed in previous lixisenatide clinical studies covering daily doses up to 60 µg, and in the FRC phase 2 study ACT12374 with daily doses up to 60 U of insulin glargine/30 µg of lixisenatide and the completed phase 3 program did not reveal findings or concerns precluding the continuation of clinical development. Given the safety profile observed in completed studies, combined treatment of insulin glargine and lixisenatide in a fixed ratio solution is considered well tolerated and reflective of the individual components, with no new risk identified for the population to be included in study EFC13794. Therefore, the risk for patients participating in this study, using daily doses up to 60 U of insulin glargine/20 µg of lixisenatide is considered limited.

All patients entering this study will receive treatment with FRC or GLP-1 receptor agonist both on top of OAD therapy (metformin ± pioglitazone ± SGLT2 inhibitors). In addition, all patients will benefit from close management of their T2DM. Rescue therapy is planned and described in the clinical study protocol for patients whose glycemia remains poorly controlled.

Given the expected improvement of metabolic control and the additional measures to improve diabetes management, these benefits are considered to outweigh the potential risk associated with the FRC drug. Therefore the benefit-risk ratio for patients participating in study EFC13794 is considered favorable.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to demonstrate the superiority of the insulin glargine/lixisenatide fixed ratio combination (FRC) versus GLP-1 receptor agonist in HbA1c change from baseline to Week 26.

5.2 SECONDARY

The secondary objectives of the 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- Monitored 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.

5.3 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).

5.4 OBJECTIVES OF THE EXTENSION PERIOD

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

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

The study will be an open label, randomized, active-controlled, 2 treatment-arm, 26-week treatment duration, parallel-group, multinational and multicenter phase 3 study comparing the FRC to GLP-1 receptor agonist. At the end of the 26-week randomized period, patients from the FRC group will be invited to participate in a 26-week single arm extension. The study will recruit outpatients with T2DM. At the end of the screening period, eligible patients will be randomized to one of two treatment groups:

- FRC group;
- GLP-1 receptor agonist group.

The randomization (1:1) will be stratified by values of HbA1c at screening (<8%, ≥8%) (<64 mmol/mol, ≥64 mmol/mol) and GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations).

The study will comprise 4 periods:

1. An up-to 2-week screening period;

- Eligible patients continue their GLP-1 RA (Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity®) on top of metformin ± pioglitazone ± SGLT2 inhibitors at the same doses/dose regimens as before the screening visit.

2. A 26-week open-label randomized treatment period;

- Eligible patients will be randomized at V3 to either receive the FRC on top of metformin ± pioglitazone ± SGLT2 inhibitors or to continue on GLP-1 receptor agonist on top of metformin ± pioglitazone ± SGLT2 inhibitors.

3. A 26-week single-arm extension period

- For patients treated with the FRC during the randomized period;
After the end of the randomized treatment period (Week 26) patients will continue to use the FRC during the next 26 weeks of the extension period. Patients on rescue therapy during the randomized period and still having their HbA1c >8% at Week 22 and the patient who discontinued prematurely from treatment before Week 26 will not be invited to participate in the extension period.
- For patients treated with GLP1-RA during the randomized period.
Patients will not be invited to participate in the extension period and will be prescribed the most appropriate antidiabetic treatment at the Investigator's discretion.

4. A post-treatment follow-up period:

Patients who will not participate in the extension period will perform the safety follow up Visit 3 days after Week 26 except those who prematurely and permanently discontinue IMP administration during the randomized treatment period but continue in the study up to the scheduled date of study completion. Patients receiving weekly GLP-1 RAs will perform the safety follow-up 9 days after Week 26.

Patients who will participate in the extension period will perform the safety follow up visit 3 days after Week 52 except those who prematurely and permanently discontinue IMP administration during the extension period but continue in the study up to the scheduled date of study completion.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum study duration per patient will be approximately 29 weeks for the patients in the GLP1-RA arm (2 weeks for the screening period followed by 26 weeks for the randomized treatment period and + 3 days post-treatment safety follow up period), and 55 weeks for the patients in the FRC arm (including a 26-week extension period) as per description provided in [Section 6.1](#).

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as Data Base Lock (DBL) instead of the usual “last patient last visit” as some delay in data integration into the data base after the “last patient last visit” might be anticipated due to the Committees’ reviews.

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study.

The primary analysis of the efficacy and safety will be 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.

6.4 STUDY COMMITTEES

6.4.1 Steering Committee

The Steering Committee is composed of scientists with clinical and methodological expertise in diabetes and conduct of clinical trials. This Committee, led by a Chairman, is responsible for producing and conducting a scientifically sound study and for ensuring accurate reporting of the

study. In that capacity, the Steering Committee must address scientific issues encountered during the study. A detailed charter describes the Steering Committee procedures.

6.4.2 Allergic Reaction Assessment Committee (ARAC)

Since lixisenatide, liraglutide, exenatide, albiglutide, and dulaglutide are peptides that may potentially generate allergic reactions; an Allergic Reaction Assessment Committee (ARAC) has been set up. The ARAC is a committee of experts in the field of allergy, independent from the Sponsor and the Investigators, implemented to assess allergic reactions or allergic-like reactions that may occur during the study. The mission of the ARAC will be to adjudicate, in a timely manner, all allergic, or possible allergic events. The ARAC will review the reported cases in a blinded manner, and based on the information reported by the Investigator, confirm whether or not the event is allergic in nature. A detailed charter describes the ARAC procedures.

6.4.3 Pancreatic Safety Assessment Committee (PSAC)

Potential safety signals for acute pancreatitis have been identified in the post-marketing experience with other GLP-1 receptor agonists. Specific monitoring for pancreatic events is planned in this study (see [Section 10.6.4](#)) and a Pancreatic Safety Assessment Committee (PSAC) has been set up. This is a committee of experts in the field of pancreatitis and pancreatic neoplasm, independent from the Sponsor and the Investigators, implemented to assess pancreatic events that may occur during the study. The PSAC will review selected pancreatic events, including pancreatitis, pancreatic neoplasms and abnormal levels of amylase or lipase. This review will be conducted in a blinded manner with regard to study treatment. A detailed charter describes the PSAC procedures.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Patients with type 2 diabetes mellitus diagnosed at least one year prior to screening visit;
- I 02. Patients who have been treated with one of the following GLP-1 receptor agonists for at least 4 months prior to screening visit (V1), and with stable dose for at least 3 months prior to screening visit (V1):
- Liraglutide (Victoza®) 1.8 mg QD or 1.2 mg QD, if 1.8 mg QD is not well tolerated according to Investigator's judgment;
 - or Exenatide BID (Byetta®) 10 µg BID or of 5 µg BID, if 10 µg BID is not well tolerated according to Investigator's judgment;

in combination with metformin (daily dose \geq 1500 mg/day or Maximum Tolerated Dose [MTD]), with or without pioglitazone, with or without SGLT2 inhibitor, all at stable dose for at least 3 months prior to screening;

or

Patients who have been treated with stable dose of one of the following GLP-1 receptor agonists for at least 6 months prior to screening visit (V1):

- Exenatide extended-release (Bydureon®) 2 mg once weekly (QW), if well tolerated according to Investigator's judgment;
- Albiglutide (Tanzeum®) 50 mg QW or 30 mg QW, if 50 mg QW is not well tolerated according to Investigator's judgment;
- Dulaglutide (Trulicity®) 1.5 mg QW or 0.75 mg QW, if 1.5 mg QW is not well tolerated according to Investigator's judgment;

in combination with metformin (daily dose \geq 1500 mg/day or MTD), with or without pioglitazone, with or without SGLT2 inhibitor, all at stable dose for at least 3 months prior to screening;

- I 03. Signed written informed consent.

7.1.1 Inclusion criteria for the extension phase

- I 04. Patients treated with FRC during the 26-week randomized treatment period.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections.

7.2.1 Exclusion criteria related to study methodology

- E 01. At screening visit, age under legal age of adulthood;
- E 02. At screening visit, HbA1c <7% (53 mmol/mol) and >9% (75 mmol/mol);
- E 03. At screening visit, Body Mass Index (BMI) ≤ 20 or >40 kg/m²;
- E 04. History of hypoglycemia unawareness;
- E 05. History of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening visit;
- E 06. Any use of anti-diabetic drugs within 3 months prior to screening visit (V1) other than those described in I 02;
- E 07. Previous treatment with insulin in the year prior to screening visit (V1) (note: short term treatment with insulin (≤ 10 days) due to intercurrent illness including gestational diabetes is allowed at the discretion of the study physician);
- E 08. Use of systemic glucocorticoids (excluding topical and inhaled forms) for a total duration of 10 days or more within 3 months prior to screening visit;
- E 09. Use of weight loss drugs within 3 months prior to screening visit; or any history of bariatric surgery;
- E 10. Use of any investigational drug within 1 month or 5 half-lives, whichever is longer, prior to screening visit;
- E 11. Personal or immediate family history of medullary thyroid cancer (MTC) or genetic conditions that predispose to MTC (eg, multiple endocrine neoplasia type 2 syndromes);
- E 12. Within the last 6 months prior to screening visit: history of stroke, myocardial infarction, unstable angina, or heart failure requiring hospitalization;
- E 13. Planned coronary, carotid or peripheral artery revascularization procedures to be performed during the study period;
- E 14. Known history of drug or alcohol abuse within 6 months prior to the time of screening visit;
- E 15. Uncontrolled or inadequately controlled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >95 mmHg) at screening visit (V1);

E 16. Conditions/situations such as:

- Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint (eg, hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products within the last 3 months prior to the screening visit);
- Patients with conditions/concomitant diseases precluding their safe participation in this study (eg, malignant tumor within 5 years prior to screening visit (V1), major systemic diseases, presence of clinically significant diabetic retinopathy or presence of macular edema likely to require treatment within the study period);
- Impossibility to meet specific protocol requirements (eg, scheduled visits, patients unable to fully understand patient's study documents and to complete them);
- Patient is uncooperative or has a condition that could lead to non-compliance with the study procedures (eg, patient unable or unwilling to do self-injections or blood glucose monitoring using the sponsor-provided blood glucose meter at home);
- Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol;
- Patients with short life expectancy;
- Requirement for concomitant treatment that could bias primary evaluation.

E 17. Laboratory findings at the screening visit:

- Fasting Plasma Glucose (FPG) >250 mg/dL (13.9 mmol/L);
- Amylase and/or lipase: >3 times the upper limit of the normal (ULN) laboratory range,
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST): >3 ULN;
- Total bilirubin >1.5 ULN (except in case of Gilbert's syndrome);
- Calcitonin \geq 20 pg/mL (5.9 pmol/L);
- Hemoglobin <10.5 g/dL or neutrophils <1,500/mm³ or platelets <100,000/mm³;
- Positive test for Hepatitis B surface antigen (HBsAg) and/or Hepatitis C antibody (HCAb);
- Positive serum pregnancy test in females of childbearing potential.

E 18. Patient who has renal function impairment with estimated glomerular filtration rate (GFR) <30 mL/min/1.73m² (using the MDRD [[Appendix A](#)]) or end-stage renal disease;

E 19. Any technical/administrative reason that makes it impossible to randomize the patient in the study;

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

- E 20. Any contraindication to metformin or pioglitazone or SGLT2 inhibitor (when applicable) use, according to local labeling;
- E 21. Any contraindication to liraglutide (Victoza®) use, according to local labeling. History of hypersensitivity to liraglutide (Victoza®) or any product components;
- E 22. Any contraindication to exenatide (Byetta®) use, according to local labeling. History of hypersensitivity to exenatide (Byetta®) or any product components;
- E 23. Any contraindication to exenatide extended-release (Bydureon®) use, according to local labeling. History of hypersensitivity to exenatide extended-release (Bydureon®) or any product components;
- E 24. Any contraindication to albiglutide (Tanzeum®) use, according to local labeling. History of hypersensitivity to albiglutide (Tanzeum®) or any product components;
- E 25. Any contraindication to dulaglutide (Trulicity®) use, according to local labeling. History of hypersensitivity to dulaglutide (Trulicity®) or any product components.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound (insulin glargine/lixisenatide fixed ratio combination)

- E 26. Pregnant or breastfeeding woman;
- E 27. Woman of childbearing potential not protected by highly-effective method(s) of birth control (as defined in a local protocol amendment in case of specific local requirement and/or in the Informed Consent Form) and/or who are unwilling or unable to be tested for pregnancy;
- E 28. Clinically relevant history of gastrointestinal disease associated with prolonged nausea and vomiting, including (but not limited to): gastroparesis, unstable (ie, worsening) or not controlled (ie, prolonged nausea and vomiting) gastroesophageal reflux disease requiring medical treatment, within 6 months prior to the time of screening visit or history of surgery affecting gastric emptying;
- E 29. History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy has now been performed), pancreatitis during previous treatment with incretin therapies, chronic pancreatitis, pancreatectomy;
- E 30. Contraindication to use of insulin glargine or lixisenatide according to local labeling (if applicable). History of hypersensitivity to insulin glargine, or to any of the excipients;
- E 31. History of allergic reaction to any GLP-1 receptor agonists in the past or to metacresol.

7.2.4 Additional exclusion criteria during or at the end of screening phase before randomization

- E 32. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form);
- E 33. Despite screening of the patient, enrolment/randomization is stopped at the study level.

7.2.5 Exclusion criteria for the extension period

- E 34. Patients in the FRC arm with a rescue therapy and HbA1c >8% at Week 22;
- E 35. Patients in the FRC arm who discontinued prematurely from FRC treatment before Week 26;
- E 36. Patients in the GLP-1RA treatment arm after randomization.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

FRC and GLP-1 RA (liraglutide (Victoza®), exenatide [Byetta®], exenatide extended-release [Bydureon®], albiglutide [Tanzeum®], or dulaglutide [Trulicity®]) are considered as investigational medicinal products (IMPs).

8.1.1 Formulations

Insulin glargine/lixisenatide fixed ratio combination (FRC)

FRC is supplied as a sterile aqueous solution for subcutaneous (SC) injection in a pre-filled disposable SoloStar® pen injector (100 U/mL insulin glargine with 33 or 50 µg/mL lixisenatide depending on the pen).

Control drugs

Liraglutide (Victoza®)* is supplied as a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg. Each pen is pre-filled with 3 mL of a clear colorless solution containing 6 mg/mL of liraglutide (free-base, anhydrous) and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection (6, 7).

Exenatide (Byetta®)* is supplied for subcutaneous (SC) injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen-injector (prefilled pen). Each milliliter (mL) contains 250 micrograms (µg) synthetic exenatide, metacresol, mannitol, and glacial acetic acid and sodium acetate trihydrate in water for injection. Two prefilled pens are available to deliver unit doses of 5 µg (1.2 mL prefilled pen) or 10 µg (2.4 mL prefilled pen). Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (BID) (8, 9).

Exenatide extended-release (Bydureon®)* is supplied as a sterile powder (already diluted in pens) and administered by subcutaneous injection. Each vial or a prefilled pen contains 2 mg exenatide, polylactide-co-glycolide, sucrose, carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, water for injection (sodium hydroxide may be added during manufacture of pens for pH adjustment). Each pen is a single dose of 2 mg to be injected once a week (10, 11).

Albiglutide (Tanzeum®)* is supplied as a sterile powder diluted in pens and administered by subcutaneous injection. 30-mg Pen for injection (for subcutaneous use) contains 40.3 mg lyophilized albiglutide and 0.65 mL Water for Injection diluent designed to deliver a dose of 30 mg in a volume of 0.5 mL after reconstitution. 50-mg Pen for injection (for subcutaneous use) contains 67 mg lyophilized albiglutide and 0.65 mL Water for Injection diluent designed to deliver a dose of 50 mg in a volume of 0.5 mL after reconstitution. Inactive ingredients include

153 mM mannitol, 0.01% (w/w) polysorbate 80, 10 mM sodium phosphate, and 117 mM trehalose dihydrate. Each pen is a single dose of 30mg or 50mg to be injected once a week (12).

Dulaglutide (Trulicity®)* is supplied as a sterile solution in pens and administered by subcutaneous injection. Each single dose pen contains 0.75 mg dulaglutide/0.5 mL solution or 1.5 mg dulaglutide/0.5 mL solution with following excipients: citric acid anhydrous (0.07 mg), mannitol (23.2 mg), polysorbate 80 (0.10 mg), trisodium citrate dihydrate (1.37 mg), water for injection. Each pen is a single dose of 0.75mg or 1.5mg to be injected once a week (13, 14).

*If available at country level

8.1.2 Injection devices and training for insulin glargine/lixisenatide fixed ratio combination

8.1.2.1 Pen-Injector devices

The FRC product will be self-administered with a pre-filled disposable SoloStar® pen-injector.

The dose of the FRC is titrated according to the patient's need for insulin glargine, while respecting the minimum and maximum lixisenatide dose of 5 to 20 µg/day. Note that only the dose of insulin glargine appears in the pen dosing window. The dose (µg) of lixisenatide does not appear in the dose window even though lixisenatide is pre-mixed in the cartridge. The lixisenatide dose is increased or decreased along with the insulin glargine dose changes, and the amount of change depends on which Pen (peach yellow or olive green) is used.

There are two pens (peach and olive) with different insulin glargine/lixisenatide fixed ratios which allow insulin glargine titration from 10 to 60 U while limiting lixisenatide dose to a maximum of 20 µg/day:

- **Peach Pen:** pre-filled disposable SoloStar® pen injector containing 3 mL of sterile solution of 100 U/mL insulin glargine and 50 µg/mL lixisenatide in a ratio of 2:1 (2 units of insulin glargine per 1 µg lixisenatide, glycerol [REDACTED], methionine, meta-cresol, zinc [REDACTED], HCl/NaOH and water for injection). This pen allows administration of daily combination doses between 10 U/5 µg and 40 U/20 µg in increments of 1 unit; the Peach Pen will be the pen used for starting the combination treatment.

It is theoretically possible to dial less than 10 U (corresponding to less than 10 U insulin glargine), or to deliver more than 40 U (corresponding to more than 40 U of insulin glargine) by splitting the dose into 2 separate injections (e.g. giving 2 sequential injections of 25 U each). With the Peach Pen, no doses below 10 U or above 40 U should be given. All doses should be given as 1 single injection and never split into more than 1 injection per day.

Each Peach Pen is specifically labeled for use in the study and contains in total 300 units of insulin glargine and 150 µg of lixisenatide in 3 mL.

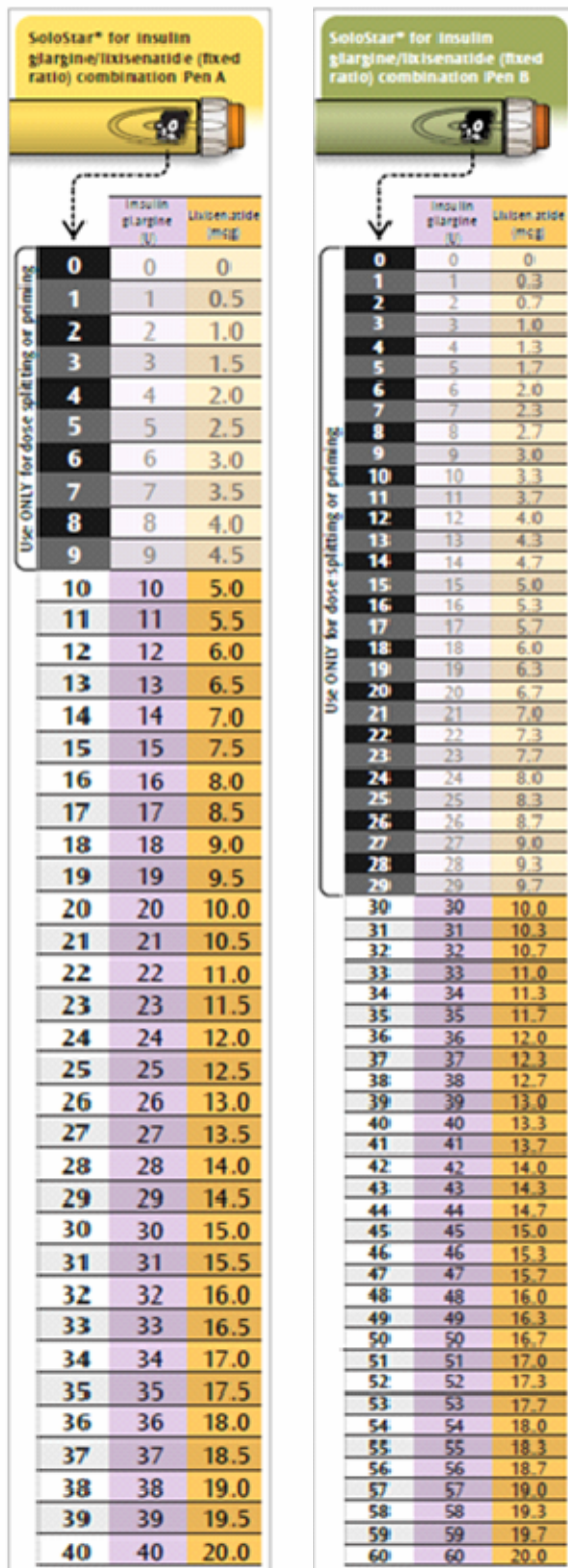
- **Olive Pen:** pre-filled disposable SoloStar® pen injector containing 3 mL of sterile solution of 100 U/mL insulin glargine and 33 µg/mL lixisenatide in ratio of 3:1 (3 units of insulin glargine per 1 µg lixisenatide, glycerol [REDACTED], methionine, meta-cresol, zinc [REDACTED], HCl/NaOH and water for injection). This pen allows administration of daily combination doses between 30 U/10 µg and 60 U/20 µg in increments of 1 unit (dose step).

It is theoretically possible to dial less than 30 U (corresponding to less than 30 U insulin glargine), or to deliver more than 60 U (corresponding to more than 60 U insulin glargine) by splitting the dose into 2 separate injections (e.g. giving 2 sequential injections of 35 U each). With the Olive Pen, no doses below 30 U or above 60 U should be given. All doses should be given as 1 single injection and never split into more than 1 injection per day.

Each Olive Pen is specifically labeled for use in the study and contains in total 300 units of insulin glargine and 99 µg of lixisenatide in 3 mL.

The lixisenatide dose is increased or decreased along with insulin glargine dose and also depends on which pen (Peach Pen or Olive Pen) is used. For example, when the dose window in the Peach Pen (ratio of 2:1) shows 30 U, this is a dose of 30 U of insulin glargine and 15 µg of lixisenatide, while for the Olive Pen (ratio of 3:1) when the dose window shows 30 U, this is a dose of 30 U of insulin glargine and 10 µg of lixisenatide.

Detailed doses for Peach Pen and Olive Pen are shown in the picture below:



8.1.2.2 Training for injection devices

An instruction leaflet will be provided which explains how to use the disposable pen-injectors. All patients will be trained by study staff on how to use the pen correctly, how to store it and how to change the needle for both the following pen-injector devices:

At V3, the patients randomized in the FRC treatment group will be trained on using both fixed ratio combination pens (peach pen and olive pen).

Training will be repeated as often as deemed necessary by study site staff during the treatment period.

The pens and leaflet that the patient will need to use during the treatment period will be dispensed according to the visit. Each patient is supplied with the appropriate number of pen-injectors according to the dispensing scheme indicated in the study flowchart (see [Section 1.2](#)).

The following commercial pen needles will be provided for use with the disposable injection pen devices:

Becton, Dickinson and Company 31 G x 8 mm	Fixed-ratio combination Peach Pen Fixed-ratio combination Olive Pen Byetta® Victoza®
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For Bydureon® and Tanzeum®, the needles are included in the treatment box. For Trulicity®, the needle is included in the pen device.

A Device-Related Event Questionnaire (DREQ) in the electronic case report form (e-CRF) should be completed if a Device Related Event (DRE) occurs. For Device Related Events that are not resolved by further guidance/review of instructions or troubleshooting with the pen during the visit (on site visit or phone visit), a Product Technical Complaint (PTC) form which is described in a separate manual must be completed, the pen associated with the event should be retrieved and both should be sent to the manufacturing site for technical investigation (Please see details in [Section 10.6.8](#)).

8.1.3 Dose schedule

Insulin glargine/lixisenatide fixed ratio combination (FRC)

The FRC should be self-administered once daily in the morning in the hour (0 to 60 minutes) before breakfast, using Peach Pen or Olive Pen depending on the daily dose of insulin glargine.

Victoza®

Liraglutide (Victoza®) will be administered as per local labelling (such as SmPC in the European Union or PI in the US), continuing the same dose schedule as before randomization. Victoza® can be administered once daily at any time of day, independently of meals.

Byetta®

Exenatide BID (Byetta®) will be administered as per local labelling (such as SmPC in the European Union or PI in the US), continuing the same dose schedule as before randomization. Byetta® can be administered twice daily at any time within the 60 minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). Byetta® should not be administered after a meal.

At days of on-site visits, the IMP which is to be administered before breakfast should be self-administered at the investigational site under the observation of site staff.

Bydureon®

Exenatide extended-release (Bydureon®) will be administered as per local labelling (such as SmPC in the European Union or PI in the US), continuing the same dose schedule as before randomization. Bydureon® can be administered once a week at any time of day, independently of meals.

Tanzeum®

Albiglutide (Tanzeum®) will be administered as per local labelling (such as SmPC in the European Union or PI in the US), continuing the same dose schedule as before randomization. Tanzeum® can be administered once a week at any time of day, independently of meals.

Trulicity®

Dulaglutide (Trulicity®) will be administered as per local labelling (such as SmPC in the European Union or PI in the US), continuing the same dose schedule as before randomization. Trulicity® can be administered once a week at any time of day, independently of meals.

Injection site

The IMP should be administered by deep subcutaneous injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall or thighs or upper arms. Within a given area, location should be changed (rotated) at each time to prevent injection site skin reactions

8.1.4 Starting dose and dose adjustment

8.1.4.1 *Insulin glargine/lixisenatide fixed ratio combination (FRC) group*

Starting dose

Treatment will be initiated with the Peach Pen. The initial daily dose of FRC to be administered will be 10 U: this corresponds to an initial associated dose of 10 U of insulin glargine and 5 µg of lixisenatide according to the 2 U/1 µg fixed ratio used in the Peach Pen.

Patients who are randomized from once weekly formulations of GLP-1 RA to the FRC group must not administer the first dose of FRC until at least 1 week after their last dose of once weekly GLP-1 RA.

Dose adjustment

During the first 8 weeks of treatment, from V3 (Week 0) to V19 (Week 8), the dose will be titrated twice a week as far as possible (see below algorithm in [Table 1](#)) based on the insulin glargine dose, until the patient reaches a target fasting SMPG of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. Titration will be done at the scheduled weekly visits (V5, V7, V9, V11, V13, V15, V17, V19) plus at one additional weekly titration phone call visit to be scheduled between the weekly visits (V4, V6, V8, V10, V12, V14, V16, V18). The additional titration phone call visit should be scheduled to allow for at least two days in between successive visits (example: weekly visits to occur on Mondays and titration phone calls to occur on Thursdays or Fridays). In case the additional phone call is missed during the week, the titration should continue as per the originally planned schedule. Thereafter, from V19 (Week 8) until V28 (Week 26), the dose will be adjusted as necessary to maintain this fasting SMPG target, with recommendation to evaluate the dose at least once a week. Twice a week titration can be continued if deemed appropriate by the investigator.

During the extension period (Week 26 to Week 52) patients treated with the FRC during the randomized period will continue their FRC treatment with the same dose regimen and dose adjustment algorithm as during the randomized treatment period.

Dose changes are based on the lowest fasting SMPG value from the last 3 measurements, which may include the value measured on the day of titration, measured by the patient using glucometers and accessories supplied by the sponsor. **However, sound clinical judgment is to be exercised during titration and investigators may decide to further up titrate if the lowest value from the last 3 measurements is between 80 and 100 mg/dL but the two other values are well above 100 mg/dL, if they believe that is an appropriate intervention in the best interest of the patient.**

Investigators may adjust or stop titration, or temporarily reduce dose if they believe further titration would be hazardous at that time.

The total daily dose will be capped at 60 U. In case a dose >60 U is needed to maintain glucose parameters below the threshold value defined for rescue therapy, the dose should be kept at 60 U and a rescue therapy should be introduced (see [Section 8.2.3](#) on rescue therapy).

Table 1 - Dose adjustment algorithm for insulin glargine/lixisenatide fixed ratio combination

The lowest fasting SMPG value from the last 3 measurements, which may include the value measured on the day of titration	FRC dose adjustments (U/day)
>140 mg/dL (>7.8 mmol/L)	+4
>100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L)	+2
Glycemic target: 80 to 100 mg/dL (4.4 and 5.6 mmol/L), inclusive	No change
≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	-2
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week.	-2 to -4 or at the discretion of the Investigator or medically qualified designee

In the insulin glargine fixed ratio combination group: choice of Peach Pen or Olive Pen

- If the patient needs a FRC dose of 10 to 40 U, use the Peach Pen (insulin glargine/lixisenatide 2:1).
- If the patient needs a FRC dose of 41 to 60 U, use the Olive Pen only (insulin glargine/lixisenatide 3:1).
- Daily doses of FRC higher than 60 U must not be administrated.

In case additional therapy (eg, a dose >60 U is needed to maintain HbA1c below the predefined threshold value (8% at 12 weeks treatment and thereafter)), the dose should be kept at 60 U and a rescue therapy should be introduced (see [Section 8.2.3](#)). All assessments planned at the end of treatment visit (V28 or V35 for the randomized treatment or extension period, respectively) are to be performed before initiating rescue therapy.

Patients will be educated regarding the titration schedule so that they will be able to monitor the titration with the assistance of the Investigator or medically qualified designee. Patients will be allowed to increase the dose by themselves if necessary (ie, if the lowest fasting SMPG value from the preceding 3 measurements, which may include the value measured on the day of titration, is >100 mg/dL), but not more than a maximum dose increase of +2 U and not more often than twice a week. All other dose increases must be discussed between the patient and appropriate site personnel. All discussions must be properly documented in the patient's record. If needed, additional contacts will be made available for patients to discuss dose adjustments in between the scheduled visits. It is at the discretion of the Investigator to allow well-trained patients to make their IMP insulin dose adjustments in between the scheduled visits without prior consultation of the site personnel.

Doses may be reduced or modified at any time for hypoglycemia. Patients who experienced mild to moderate hypoglycemia as a result of a missed meal, unusual exercise or alcohol use will be counseled on the correction of those behaviors and will not necessarily have their insulin dose decreased (decision to be based on Investigator's clinical judgment).

FRC titration monitoring

Data relevant for the FRC dose titration (eg, fasting SMPG, daily insulin dose, hypoglycemia occurrence) will be reviewed by dedicated persons regularly to identify patients whose FRC dose was not titrated according to the recommended dose adjustment algorithm. If needed, re-training of site staff (including investigator) on titration will be performed. The details on FRC titration monitoring will be provided in separate documents.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Background therapy

Background OAD treatment metformin, pioglitazone and SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are considered as non-investigational medicinal products (NIMPs).

Patients are enrolled with a background therapy consisting of metformin alone or metformin and pioglitazone or metformin and SGLT2 inhibitor combination or triple combination. Metformin and pioglitazone (if applicable) and SGLT2 inhibitors (if applicable) should be administered orally according to local product labeling. 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). The doses of background OAD treatment should be continued and should remain stable throughout the study unless there is a specific safety issue related to this treatment.

The rescue therapy is also a NIMP and its introduction is described in [Section 8.2.3](#). As per rescue therapy criteria rapid acting insulin is suggested (insulin glulisine when available) for patients in the FRC arm or basal insulin for patients in the GLP-1 RA arm are suggested.

Background therapy or rescue therapy are to be reported in the electronic case report form (e-CRF).

The cost of the permitted background OAD treatment and suggested rescue therapy, if not covered by health insurance, will be reimbursed where permitted by local regulations.

8.2.2 Diet and Exercise

Lifestyle and diet therapy provided before the time of screening is to be continued during the study. Dietary and lifestyle counseling will be given by a healthcare professional at V2 or V3, V21, V28 and V32 which should be consistent with international or local guidelines for type 2 diabetic patients (with regard to the distribution of calories among carbohydrates, proteins, and fats, exercise, etc).

Compliance with the diet and lifestyle counseling will be assessed in case of insufficient glucose control.

8.2.3 Rescue Therapy

In case **HbA1c is above 8% at Week 12 or later on**, the Investigator will receive an alert issued by the central laboratory and should ensure that no reasonable explanation exists for insufficient glucose control and in particular that there is no intercurrent disease which may jeopardize glycemic control (eg, infectious disease), that the treatments are given at the planned dose and compliance to treatment and diet and lifestyle is appropriate. HbA1c assessment should be scheduled at next visit (if next visit is a phone call, it should be replaced by an unscheduled visit at site) or within 4 weeks. If appropriate corrective action fails and if the repeated HbA1c remain above 8%, a rescue therapy should be considered according to the Investigator's judgment.

In the FRC arm:

- rescue therapy is recommended only if further dose titration is not possible, ie, 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.

During the extension period, suggested rescue therapy is rapid acting insulin (insulin- glulisine when available) for all patients.

All assessments planned at the end of the randomized treatment visit (V28) are to be performed before initiating rescue therapy during the randomized treatment period. All assessments planned at the end of extension period treatment visit (V35) are to be performed before initiating rescue therapy during the extension period. After these assessments are completed and rescue therapy initiated, the patient will remain in the study and continue to administer the study treatment (including background therapy). The planned visits and assessments should be performed until the last scheduled visit. Patients receiving rescue therapy during the randomized treatment period and eligible for the extension period can continue it as required.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

This study is an open-label design.

Compensation for lack of blinding:

The Investigator and the Sponsor will not have access to the data of the primary efficacy endpoint (ie, HbA1c) nor to the data of the standardized meal test endpoints obtained after baseline visit until the end of the study. However, the study team may review the data for the primary efficacy

parameter in descriptive statistics with the name of the IMP treatment masked during data review meetings.

ARAC, and PSAC members will review and adjudicate events in a blinded manner (please also refer to [Section 6.4](#)).

Refer to [Section 10.5](#) for suspected unexpected adverse drug reaction unblinding by the Sponsor.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients will be randomized to one of the two following treatment arms during the 26-week open-label treatment period:

- FRC once daily, or
- Victoza® once daily, Byetta® twice daily, Bydureon® once weekly, Tanzeum® once weekly, or Trulicity® once weekly (continuing whichever therapy they were taking prior to randomization).

The randomization ratio is 1:1. The randomization is stratified by HbA1c (<8%, ≥8%) at screening and GLP-1 receptor agonist subtype at screening (once/twice daily formulations, once weekly formulations).

The randomization and the treatment allocation are performed centrally by an interactive response technology (IRT). The randomized treatment kit number list is generated centrally by Sanofi, and the Study Biostatistician provides the randomization scheme (including stratification) to the IRT. Then, the IRT generates the patient randomization list according to which it allocates treatment groups to the patients.

The IMPs (FRC, or Victoza®, or Byetta®, or Bydureon®, or Tanzeum®, or Trulicity®) will be provided starting at V3 in open-label boxes and are identified with treatment kit numbers.

At the screening visit the Investigator or designee has to contact the IRT center to receive the patient number. The patient identification (patient number) is composed of a 12-digit number containing the 3-digit country code, the 4-digit center code and the 5-digit patient chronological number (which is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center, etc).

A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The appropriate number of kits will be dispensed to cover up to the next dispensing visit (please refer to [Section 1.2](#)).

Kits fixed-ratio combination 2 U/1 µg	1 open label kit contains 3 peach pens prefilled with a solution of 100 U/mL insulin glargine and 50 µg/mL lixisenatide labelled in randomized conditions on the box only.
Kits fixed-ratio combination 3 U/1 µg	1 open label kit contains 3 olive pens prefilled with a solution of 100 U/mL insulin glargine and 33 µg/mL lixisenatide labelled in randomized conditions on the box only.
Kits Byetta® 5 µg	1 open label kit contains 1 pen pre- filled with 1.2 mL of exenatide solution labelled in randomized conditions on the box only.
Kits Byetta® 10 µg	1 open label kit contains 1 pen pre- filled with 2.4 mL of exenatide solution labelled in randomized conditions on the box only.
Kits Victoza®	1 open label kit contains 2 pens prefilled with a solution of 6 mg/mL liraglutide labelled in randomized conditions on the box only.
Kits Trulicity® 0.75 mg/0.5mL	1 open label kit contains 4 single dose pens prefilled with a solution of 0.75 mg/0.5mL dulaglutide labelled in randomized conditions on the box only.
Kits Trulicity® 1.5 mg/0.5mL	1 open label kit contains 4 single dose pens prefilled with a solution of 1.5 mg/0.5mL dulaglutide labelled in randomized conditions on the box only.
Kits Bydureon® 2 mg	1 open label kit contains 4 blisters containing 1 single dose pens with 2 mg of exenatide extended release and 1 needle. An extra needle is supply in the kit labelled in randomized conditions on the box only.
Kits Tanzeum® 30 mg	1 open label kit contains 4 single dose pens prefilled with 30 mg/ 0.5 mL of albiglutide + 4 needles. The kit is labelled in randomized conditions on the box only.
Kits Tanzeum® 50 mg	1 open label kit contains 4 single dose pens prefilled with 50 mg/ 0.5 mL of albiglutide + 4 needles. The kit is labelled in randomized conditions on the box only.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The expiry date is mentioned on the IMPs labels, and storage conditions are written on the IMPs labels and in the instruction leaflet.

Insulin glargine/lixisenatide fixed ratio combination

Prior to the first use, the FRC cartridges have to be stored between +2°C and +8°C, protected from light, and must not be frozen.

In-use disposable pen-injectors have to be stored below +30°C (not refrigerated) protected from light. Each pen should be replaced if not completely used within 14 days.

Victoza®

Prior to first use, Victoza® should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C). After first use, the Victoza® pen can be kept at controlled room (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C).

Victoza® should be protected from light, must not be frozen, and must not be used if it has been frozen. The pen should be replaced if not completely used within 30 days.

Byetta®

Prior to first use, Byetta® must be stored in the refrigerator at 36°F to 46°F (2°C to 8°C). After first use, the Byetta® pen can be kept at a temperature not to exceed 77°F (25°C).

Byetta® should be protected from light, must not be frozen, and must not be used if it has been frozen. The pen should be replaced if not completely used within 30 days.

Bydureon®

Bydureon® should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C) and protected from light until prepared for use. It must not be frozen and must not be used if it has been frozen.

If needed, Bydureon® can be kept out of the refrigerator at 68°F to 77°F (20°C to 25°C) for up to 4 weeks.

Bydureon® must be administered immediately after the exenatide powder is suspended in the diluent.

Tanzeum®

Tanzeum® should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C), must not be frozen, and must not be used if it has been frozen.

If needed, Tanzeum® pens can be stored in the box at room temperature below 86°F (30°C) for up to 4 weeks prior to use.

A pen must be used within 8 hours after reconstitution.

Trulicity®

Trulicity® should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C), protected from light, must not be frozen, and must not be used if it has been frozen.

If needed, each single-dose pen can be kept at room temperature, not to exceed 86°F (30°C) for a total of 14 days.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator checks the compliance to the study treatments based on the patient diary and by visually checking the returned FRC pens, Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity® pens and completes the appropriate "Treatment Log Form". Visual check on return has to be performed by site staff. In addition he/she also records the dosing information on the appropriate pages of the e-CRF. The monitor in charge of the study then checks the e-CRF data by comparing them with the IMP which he/she has retrieved and treatment log forms.

For background OADs, name, start and end date of treatment, total daily dose, etc, will be documented in the source documents. Compliance to background OADs will be checked by interviewing the patient and reviewing the diary at each visit and will be documented in the source documents and in the e-CRF.

8.7.2 Return and/or destruction of treatments

Patients have to return all the used and in-use IMP (and corresponding leaflets if appropriate) at each on-site visit. Patients should also return the unused IMP each time a re-supply is planned (see [Section 1.2](#)).

Patients have to return all the used, in-use and unused IMP at V28 (or final assessment on treatment visit in case of permanent premature discontinuation).

All used, partially used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

For NIMP not provided by the Sponsor, tracking and reconciliation will be managed according to local regulation.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

8.8.1 Allowed concomitant therapy

Any therapies or medications other than prohibited concomitant therapy in addition to the IMP should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator, with a stable dose (when possible).

In the FRC treatment group, for oral treatments that are dependent on threshold concentrations for efficacy, such as oral contraceptives and antibiotics, patients should be advised to take those treatments at least 1 hour before study drug injection or about 11 hours after study drug injection. Gastro-resistant formulations containing substances sensitive to stomach degradation should also be administered 1 hour before or about 11 hours after injection of the FRC.

Specific treatments, which are ongoing before the study and/or prescribed or changed during the study, must be recorded in the e-CRF and Source Data (please refer to [Section 10.2.1](#)).

8.8.2 Concomitant diabetes therapy

Background OADs (metformin, and pioglitazone and SGLT2 inhibitors) are non-investigational background therapies authorized during the study. Please see [Section 8.2.1](#) for details.

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. Please see [Section 8.2.3](#) for details.

No other concomitant antidiabetic treatments except the authorized background and rescue therapies described above should be used in this study.

8.8.3 Prohibited concomitant therapy

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

- Any glucose-lowering agents other than the IMP, authorized background OADs and rescue therapy, if necessary;
- **Note:** Short-term use (≤ 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.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

All biological efficacy and safety analyses will be performed by a Central Laboratory. Detailed information on samples drawing, management and analysis will be provided in a specific manual.

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

- Change in HbA1c from baseline to Week 26.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoint(s)

- Percentage of patients reaching HbA1c <7 % (53 mmol/mol) or ≤6.5% (48 mmol/mol) at Week 26;
- 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;
- Percentage of patients requiring rescue therapy during the 26 weeks treatment period;
- Change in body weight from baseline to Week 26.

9.2.1.1 *Observation period of efficacy endpoints*

All scheduled measurements collected during the study period will be used in the analysis, including those obtained after IMP discontinuation or rescue medication use.

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 day for standardized meal test parameters,

7-point SMPG; 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.

- 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.

9.2.1.2 Efficacy Assessment Methods

9.2.1.2.1 HbA1c measurement

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I “National Glycohemoglobin Standardization Program” (NGSP) central laboratory.

9.2.1.2.2 Standardized meal test

Patients will undergo a standardized meal challenge to assess fasting and postprandial glucose (central laboratory), as well as plasma glucose excursion at V2 (Week -1) and V28 (Week 26), as well as V35 (Week 52) for patient continuing in the extension period.

The standardized meal contains approximately 600 kcal and is composed of 50 to 55% carbohydrate, 15 to 20% protein and 25 to 30% fat. The composition and the quantity of the standardized meal must be identical throughout the study.

If the patient needs to receive a rescue antidiabetic medication, the standardized meal test should be performed before the introduction of the rescue medication and will not be performed at the final on-treatment visit.

In case of permanent discontinuation of IMP, the standardized meal test should be performed only if the patient receives IMP on the day of the visit for daily IMP, or one to three days after the injection of the weekly GLP1-RA, and will not be repeated at the final on-treatment visit (Week 26 or Week 52).

On the day of the standardized meal test, the patients will come to the investigational site in the morning, in fasting conditions for at least 8 hours (no food or drink during this time except water), before the scheduled standardized meal test. At V28 (Week 26) and V35 (Week 52) injection of

FRC or Byetta® (patients injecting Byetta® before breakfast) should be done at the investigational site 30 minutes before the start of the standardized meal. Patients taking Bydureon®, Tanzeum®, or Trulicity® should inject their medication as per their usual weekly schedule. The meal test should be preferably performed from one to three days after the injection of the weekly GLP1-RA.

The standardized meal for all patients should be consumed within a 15-minute period.

Blood for plasma glucose and C-peptide is drawn 6 times:

- 30 minutes prior to the start of the meal and before IMP administration if done before breakfast;
- Just before the start of the standardized meal (0 minute);
- 30 minutes after the start of the standardized meal;
- 60 minutes after the start of the standardized meal;
- 90 minutes after the start of the standardized meal;
- 120 minutes after the start of the standardized meal.

The exact times of the IMP injection and the standardized meal intake and the blood draws are to be documented.

9.2.1.2.3 *Self-monitored plasma glucose profiles (SMPG) and glucometer*

9.2.1.2.3.1 Self-monitored plasma glucose profiles (SMPG)

SMPG measurements are included the followings and applies for all treatment groups:

Fasting SMPG

Fasting SMPG will be used by the Investigator and patients if appropriate to titrate and adjust the FRC dose and to monitor glycemic control in all groups. For all patients (FRC arms and GLP-1 RA control arm), the fasting SMPG should be measured by the patient before taking breakfast and administering the glucose-lowering agents:

- once a day from randomization/IMP allocation V3 (Week 0) until V19 (Week 8) inclusive;
- at least three times per week from V19 (Week 8) until the end of the randomized treatment visit V28 (Week 26) inclusive for all patients, and from V28 (Week 26) until the end of the extension treatment visit V35 (Week 52) inclusive for patients participating in the extension period, and
- whenever the patient experiences hypoglycemia signs or symptoms.

Fasting SMPG values should be recorded in the patient diary.

The following daily fasting SMPG values in the FRC group will be entered in the e-CRF:

- For the first 8 weeks of the treatment period (from V3 until V19 inclusive): all available fasting SMPG values;
- After the first 8 weeks until the end of the treatment period and during extension period: at least the last 3 available fasting SMPG values from the week prior to each site or phone visit; the last 3 available values leading to IMP dose change.

The following daily fasting SMPG values in the GLP-1 RA control arm will be entered into the e-CRF:

- For the first week of the treatment period (from V3 until V5 inclusive): all available fasting SMPG values;
- After the first week until the end of the treatment period: at least the last 3 available fasting SMPG values from the week prior to each on site visit (V11, V19, V21, V24, V26, V28).

7-point SMPG Profile

The 7-point SMPG profile should be measured at the following 7 points: pre-prandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime. Two hours postprandial (breakfast, lunch and dinner) is defined as 2 hours after the start of the meal.

The patients are requested to perform 7-point SMPG profile measurement over a single 24-hour period on 2 different days in the week before V3 (Week 0), V21 (Week 12), V28 (Week 26) and V35 (Week 52) for FRC patients- end of treatment assessment visit. The SMPG values measured for each 7-point SMPG profile will be recorded in the patient diary and transferred into the e-CRF.

On the 7-point profile days, information on times of meals and bedtime, injection time and doses of IMP should be recorded in the patient's diary and entered in the e-CRF.

SMPG during episodes of symptomatic hypoglycemia

Whenever the patient feels hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected ([Section 10.6.1](#)), unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation.

The SMPG values are to be entered in the patient's diary and entered in the e-CRF.

Further SMPG

The Investigator may decide to request more frequent self-monitoring of plasma glucose if he/she considers necessary for the patient. The SMPG values are to be entered in the patient's diary.

9.2.1.2.3.2 Glucometer, patient diaries and training

All patients are supplied with a glucometer, the corresponding supplies (lancets, test strips, etc), an instruction leaflet, and with diaries at visit V2 (Week -1) in order to perform self-measurement of plasma glucose and its recording. The patients will be instructed to bring their glucometers and patient diaries with them to each site visit.

The glucometers should be calibrated according to instructions given in the package leaflet, and the study site should also check the glucose meters regularly using the provided control solutions for data validity.

At visit V2 (Week -1) patients are trained to accurately measure plasma glucose values with the glucometer and to correctly record the values and other requested information in the patient's diaries. It is the Investigator's responsibility to explain the need to measure glucose at the times requested and to correctly record all SMPG values in the patient's diaries to patients. Training is repeated as often as necessary at the study visits.

Instruction on how to complete the patient diary on a daily basis will be done by site staff. At each on site visit:

- The study site staff reviews the patient's diary;
- SMPG values stored in the glucose meter memory will be downloaded, printed out, dated, signed and filed into the patient file. This information will help the Investigator to assess treatment effects, adjust insulin doses and compliance.

Note: The SMPG values recorded into the diary, which have to be entered in the e-CRF, have to be checked for consistency with the information downloaded from the glucose meter. In case of inconsistency, the reason for inconsistency has to be documented. If needed, the resulting action (eg, training of the patient on correct documentation of the values) is also to be documented. The confirmed values will be entered into e-CRF by the Investigator or designee based on the glucometer output values.

The patient diary includes but is not limited to the following information:

- Time and dose of IMP (insulin glargine/lixisenatide combination or Victoza®, or Byetta® or Bydureon®, or Tanzeum®, or Trulicity®) injections;
- Days of no IMP use (including date of starting and ending);
- Time and value of fasting SMPG measurements;
- Time of start of meals and SMPG measurements as well as plasma glucose values the days of the 7-point profile;
- Potential changes in background OADs;
- Adverse events, including signs and symptoms suggesting occurrence of hypoglycemia and local injection site reactions, if any;
- Any problems with an injection pen.

9.2.1.2.4 *Body weight*

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.

The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The patient should stand in the center of the platform as standing off-center may affect measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded in the e-CRF and Source Data. Self-reported weights are not acceptable; patients must not read the scales themselves.

9.2.1.2.5 *Dose of IMP*

The patients document daily/weekly their IMP dose(s) or any missed IMP injection(s) in the patient diary.

The following values will be entered in the e-CRF:

- GLP-1 RA (Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity®):
 - During the screening period and at randomization (V3): daily/weekly dose(s);
 - Throughout the treatment period (after V3 until V28): Any dose change(s).
- FRC:
 - From V3 to V19: daily dose and time of injection before breakfast on the day prior to each on site or phone visit;
 - After V19 and during extension period: daily dose. Time of injection to be recorded in case of change of dose;
 - Dose and time of injection on the day prior to PK sampling;
 - Dose and time of injection for any occurrence of hypoglycemia or allergic reaction;
 - Daily dose and time of injection used on the 7-point SMPG days, meal test days, and days of first and last injection of IMP.
- Missed IMP injections and overdose (if applicable);
- In case of any change in doses administered or hypoglycemia (if appropriate), the dose and injection time should be entered in the e-CRF.

9.2.1.2.6 *Fasting plasma glucose*

FPG is measured at a central laboratory. At V2, V28 and V35, FPG will be part of the standardized meal test.

9.2.2 Safety endpoints

The safety endpoints are assessed by:

- Symptomatic hypoglycemia (documented, probable, severe symptomatic hypoglycemia);
- Adverse events (AE), serious adverse events (SAE); adverse event of special interest (AESI), AEs requiring specific monitoring and reporting on specific electronic case report forms (e-CRFs) (suspected allergic reactions, patients with increased pancreatic enzymes >2 ULN/pancreatic events, patients with increased calcitonin ≥ 20 pg/mL, Device-related events (DRE));
- Safety laboratory values;
- Vital signs;
- Electrocardiogram (ECG);
- Immunogenicity (antibody variables, FRC group): anti-insulin and anti-lixisenatide antibodies.

Observation period of safety endpoints

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 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: 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, on-treatment period is defined as 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 on-treatment period for the whole study (including the 26-week 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.
- 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 for the whole study).

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

9.2.2.1 Symptomatic hypoglycemia

Symptomatic hypoglycemia (documented, probable, severe symptomatic hypoglycemia) will be assessed. Please refer to [Section 10.6.1](#) for details.

9.2.2.2 Adverse events

AE including SAE and adverse events of special interest (AESI) will be assessed. Please refer to [Section 10.4](#) to [Section 10.7](#) for details.

Adverse event collection: Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study.

9.2.2.3 Laboratory safety variables

All laboratory data listed in this section will be measured at a central laboratory. The laboratory data will be collected at designated visits in [Section 1.2](#). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. The conventional unit will be presented if appropriate.

The following laboratory safety variables will be analyzed:

- Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets;
- Clinical chemistry: total bilirubin (and, in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), creatinine, uric acid, sodium, potassium, calcium, phosphorus;
- Lipid parameters (total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides);
- Serum amylase and lipase;
- Serum calcitonin;
- Urine albumin/creatinine ratio assessment (to be done on first morning urine sample).

In addition, the following laboratory data will also be collected at screening visit, baseline visit and at on-site visits depending on the item (see [Section 1.2](#)) for identifying patients with exclusion criteria, childbearing potential or safety consideration.

- Hepatitis B surface antigen and hepatitis C antibody (only at screening);
- Urinalysis (assayed by the central laboratory): pH, glucose, ketones, leucocytes, blood/hemoglobin, protein (only at screening);
- Serum pregnancy test in females of childbearing potential;
- Serum follicle stimulating hormone (FSH) (only in females requiring confirmation of postmenopausal status, and only at screening).

In case of suspected acute pancreatitis, safety laboratory, including amylase and lipase should be performed in a timely manner. Please also refer to [Section 10.6.4](#).

Notes: Any abnormal laboratory value should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making a decision of permanent discontinuation of IMP for the concerned patient. Please also refer to [Section 10.3](#) and the “General Guidelines for reporting AEs” in [Section 10.4.2](#).

9.2.2.4 Vital signs and physical examination

Clinical safety will be assessed by:

- Physical examination;
- Vital signs (systolic and diastolic blood pressure, heart rate).

Blood pressure (mmHg) should be measured when the patient is quiet and seated and with their arm outstretched in line with mid-sternum and supported. Measurement should be taken under standardized conditions, approximately at the same time of the day, on the same arm, with the same device (after the patient has rested comfortably for at least five minutes) and the values are to be recorded in the e-CRF. Both systolic blood pressure and diastolic blood pressure should be recorded. Devices for blood pressure measurement should be regularly recalibrated according to manufacturers’ instructions.

Determination of the arm for blood pressure measurements:

At V1 of the screening period, blood pressure has to be measured on both of the arms after 5 minutes in seated position and then again after two minutes in both arms in seated position. The arm with the higher diastolic pressure will be determined at this visit, identifying the reference arm for future measurements throughout the study. The highest value will be recorded in the e-CRF (all blood pressure values are to be recorded in the source data).

Heart rate (bpm) will be measured at the time of the measurement of blood pressure.

9.2.2.5 Electrocardiogram variables

The ECG assessment of “normal” or “abnormal” will be analyzed.

Investigators will have 12-lead ECG devices which will automatically assess the ECG as “normal” or “abnormal”. ECG status of “normal” or “abnormal” will be reported in the e-CRF as determined by the Investigator.

The 12-lead ECGs should be performed after at least 10 minutes in supine position. The electrodes are to be positioned at the same place for each ECG recording throughout the study. Each trace is analyzed in comparison with the screening recorded tracing. The original tracing is kept as source data.

Notes: Any abnormal ECG parameter should be immediately rechecked for confirmation before making a decision of permanent discontinuation of treatment with IMPs for the concerned patient. Please also refer to [Section 10.3](#) and the “General Guidelines for reporting AEs” in [Section 10.4.2](#).

9.2.2.6 Immunogenicity

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.

Sampling time: Blood samples for antibodies will be taken before injection of IMP in the FRC patients: for anti-lixisenatide antibody, at baseline (V3, day 1), V11 (Week 4), V21 (Week 12) and V28 (Week 26), V35 (Week 52, for patient in extension period); for anti-insulin antibody, at baseline (V3, Day 1) and V28 (Week 26), V35 (Week 52, for patient in extension period). Samples will also be taken in case of premature discontinuation from IMP, if possible. One additional sample for potential additional assessments of immunogenicity will be taken when the patients completes the study (either at Week 26, Week 52 or in case of premature discontinuation).

Antibodies handling procedures: Detailed procedures of sample preparation, storage and shipment will be described in the specific laboratory manual.

Bioanalytical method: Antibodies will be determined at centralized laboratories using validated assay methodologies.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

Pharmacokinetics parameters: Total plasma concentrations of lixisenatide

Lixisenatide PK sampling: For total concentrations of lixisenatide, blood samples are to be taken for patients from the FRC group as described in the flowchart:

- At Day 1 one sample will be taken in the time period from 1 to 4 hours post injection.
- At the other visits (Week 4, Week 12, Week 26 and Week 52), 1 sample will be taken immediately before IMP injection and 1 sample will be taken in the time period from 1 to 4 hours post injection.

Samples will also be taken in case of premature discontinuation from IMP or rescue therapy, if possible. In case of premature discontinuation, one PK sample is sufficient if the last dose of IMP is not administered at this visit.

PK handling procedure: Detailed procedure of sample preparation, storage and shipment are described in the specific lab manual.

Bioanalytical method: For determination of total concentrations of lixisenatide (bound and unbound to anti-lixisenatide antibodies) plasma samples will be analyzed using a validated enzyme linked immuno-sorbent assay (ELISA) with a lower limit of quantification of 5.5 pg/mL.

9.3.2 Other endpoints

- Insulin glargine and lixisenatide doses at Week 26 in the combination group;
- C-peptide evaluation during standardized meal test from baseline to Week 26;
- Percentage of patients reaching HbA1c <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.

9.4 ENDPOINTS OF THE EXTENSION PERIOD

All primary and secondary efficacy, safety, PK and other endpoints will be also assessed at the end of the extension period (Week 52).

9.5 FUTURE USE OF SAMPLES

Not applicable.

9.6 APPROPRIATENESS OF MEASUREMENTS

The combination of basal insulin with a GLP-1 receptor agonist (GLP-1 RA) in a single daily injection is expected to lower HbA1c, as a result of complementary action on both fasting and postprandial glucose, with less or no weight gain compared to insulin alone, and a limited increased risk of hypoglycemia.

The primary efficacy analysis of this study comparing FRC to GLP-1 receptor agonist will be based on the primary endpoint: change in HbA1c from baseline to Week 26.

The concentration of HbA1c reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2- to 3-months. HbA1c has also been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is known to reduce the risk of long-term microvascular complications.

Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. In addition to the analysis of the change from baseline in HbA1c, the responder analysis allows the clinical relevance of the reduction observed in HbA1c to be demonstrated. The duration of study treatment is considered to be sufficient for achieving stable conditions with IMP and for enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

The problem of weight gain in type 2 diabetes is widely recognized. More than 80% of individuals with type 2 diabetes are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. In this LixiLan-G study it is postulated that treatment intensification with the combination product will overcome the burden of weight gain that is typical when adding or up titrating basal insulin. Taking into account the major impact of insulin-related body weight gain, it is appropriate to include body weight change as secondary efficacy endpoint.

Insulin glargine targets primarily, although not exclusively, fasting hyperglycemia, and lixisenatide effectively acts on post-prandial glycaemia mainly by slowing down gastric emptying. Therefore assessment of both fasting and post-prandial glucose (after a standardized meal) is relevant in this study. These 2 parameters are also considered by regulatory agencies to be supportive of efficacy of an antidiabetic agent. C-peptide, which is cleaved from insulin in secretory granules, is a known as a marker for β -cell function and will therefore be also evaluated.

Safety will be evaluated by standard clinical and laboratory measurements. Specific safety parameters of interest for a glucose lowering injectable peptide, such as symptomatic hypoglycemia, injection site reactions and potential allergic reactions, will also be assessed. In addition, due to the use of the GLP-1 receptor agonists, pancreatic enzymes (amylase and lipase) and serum calcitonin concentration will be monitored and reported over the study course according to specific procedures ([Section 10.6.4](#) and [Section 10.6.5](#)). Furthermore, assessments of the immunogenicity of insulin glargine and lixisenatide will be performed.

10 STUDY PROCEDURES

This section is to summarize information not presented in the flow chart or in [Section 9](#).

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments listed in the “Study Flow Chart” in [Section 1.2](#) are not repeated in this section. The aim of this section is to provide details on how some of the procedures/assessments have to be performed.

This is an outpatient study. The 26-week randomized period consists of 10 on-site visits, 8 titration phone calls (only for FRC arm) and 11 phone-call visits. Additional, optional phone call visits to monitor insulin glargine/lixisenatide combination dose adjustment should be scheduled whenever considered necessary by the Investigator.

During the single-arm extension period there will be 3 additional on-site visits and 4 phone call visits.

The patient has to be fasting for all on-site visits. For all these visits, the patient should be seen in the morning, at approximately the same time, as far as possible. The patient should take background OADs and inject the FRC or Victoza® or Byetta® (if injected in the morning) at the investigational site after the fasting blood sample has been drawn. Patients taking Bydureon®, Tanzeum®, or Trulicity® should follow their usual weekly injection schedule, and therefore do not necessarily need to inject at the investigational site on the day of an on-site visit.

The **fasting condition** is defined as an overnight fast no less than 8 hours that consisted of no food or liquid intake, other than water. IMP (not including the once weekly GLP-1 RAs) and other glucose-lowering agents should be administered after the fasting blood sample is drawn for all laboratory tests on the study site.

Note: If the patient is not fasting at the visits specified above, the blood sample will not be collected and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted.

Visit window: During the screening period and for randomization visit (V3) a visit window of ± 3 days is acceptable, taking the date of V1 as reference until the randomization V3. During the treatment period a visit window of ± 3 days is acceptable taking V3 as reference, for V5 to V19 (except for additional titration calls for FRC treatment, see [Section 10.1.2.4](#)), and a visit window of ± 5 days is acceptable from V20 to V35. A visit window of -1 day or + 3 days for the post-treatment follow-up visits for the randomized treatment period and extension period is acceptable using the day of V28 and V35 respectively as reference. If one visit date is changed, the next visit should take place according to the original schedule.

10.1.1 Screening period (Week -2 up to Week 0)

The screening period is about 2 weeks \pm 3 days from screening visit (V1, Week -2) to baseline visit (V3, Week 0). The screening period must be a minimum of 1 week duration in order to ensure availability of IMP at the site (IMP must be available for the site to conduct the baseline visit). It must also be long enough to collect the data to establish if the patient satisfies the inclusion/exclusion criteria.

Only patients who meet the inclusion criteria as noted in [Section 7.1](#) may be screened. It will be the Investigator's responsibility to confirm the diagnosis of T2DM.

During the screening period the patients should continue their anti-hyperglycemic treatment as before the screening visit, ie, their background therapy (please see [Section 8.2](#) for details) as well as their GLP-1 RA treatment (Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity®).

All laboratory tests measured at a central laboratory that are needed for checking the exclusion criteria of the patients are performed at the screening visit (V1). After the screening period, patients who meet the selection criteria at the end of screening period as noted in [Section 7](#) can enter into the open-label randomized treatment period. If any of the laboratory parameters are not available at the end of the screening period (eg, sample material damaged during transport...), a retest can be performed. Retesting done by the Central Laboratory for quality purposes by the reference lab for HbA1c cannot be used for screening purposes. Exceptionally, if justified according to the Investigator and after discussion with the medical monitor, this screening period can be extended by one additional week. This may occur in, but is not limited to, examples such as when source documentation (eg, from patient's primary physician) needs to be obtained to confirm the diagnosis of type 2 diabetes, when screening laboratory results demand further clarification, or in cases where there is a delay in IMP supply or when the patient requires additional training and time to demonstrate compliance. Randomization V3 (baseline, Day 1) cannot be scheduled later than 3 weeks (\pm 3 days) after the screening visit (V1, Week -2).

A patient should not be randomized more than once. In case of screen failure due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the patient can be rescreened one time for this study.

10.1.1.1 On-site visits: V1 (screening visit, Week -2); V2 (Week -1)

For the complete list and contents of procedures/assessments scheduled for the screening period, please refer to the "Study Flow Chart" in [Section 1.2](#) and for detailed description of assessments [Section 9](#) and [Section 10.6](#).

The details of the procedures/assessments to be performed at on-site visits during the screening period and which are not described elsewhere are provided below:

Informed consent

The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration at the screening visit. Written information will be

provided to the patient and must be signed by the patient and Investigator prior to any investigations.

Demography, diabetes and medical/surgical history, cardiovascular & allergy history, alcohol and smoking habits, and medications

Demography data such as birth date, gender and race will be collected. Collection of diabetes history will include documentation of duration of diabetes, history of microvascular complications (retinopathy, neuropathy, and nephropathy), and history of gestational diabetes if applicable. Medical/surgical history including patient's cardiovascular and allergy history, and patient's family diabetes history will be recorded. Data for alcohol habits during the last 12 months before screening visit and smoking habits will be collected.

Check of previous and/or current medication refers to documentation of medication including glucose-lowering agents and over-the-counter medications. Indicate specifically if lixisenatide has been previously used. In women of child-bearing potential, the contraceptive method(s) have to be documented.

Diet and lifestyle counseling

Please see [Section 8.2.2](#).

IRT contact

IRT will be contacted for notification of screening and patient number allocation ([Section 8.4](#)). Please note that it is important to have the IRT contact before any blood sample is drawn because the patient number is given by IRT and it must be reported on the laboratory requisition forms.

Glucometer dispensation and training

Please see [Section 9.2.1.2.3.2](#).

Central laboratory testing

Blood sample is drawn for all central laboratory tests needed for checking the exclusion criteria;

Provide patients with a urine container and instruct them how to collect at home in the morning of their first morning urine and to bring the urine sample to the site at planned visit.

An appointment is given to the patient for the next visit. Patients are instructed to return to the site in the morning and to bring the glucose meter and the diary.

10.1.2 Open-label randomized treatment period (Week 0 to Week 26)

Patients meeting all inclusion criteria and with no exclusion criteria at the end of the screening period are eligible to be enrolled into the open-label randomized treatment period. The duration of the open-label treatment period for all patients is 26 weeks \pm 5 days from baseline visit (V3, Week 0) to the end of treatment visit (V28, Week 26).

Each patient self-administers IMP once daily from V3 (Week 0) up to the end of the open-label treatment period (V28, Week 26) for the patients treated with FRC or Victoza®, twice daily within 60 minutes prior to a meal for patients treated with Byetta®, and once weekly for patients treated with Bydureon®, Tanzeum®, or Trulicity®. The IMP dose for the patients receiving the FRC will be adjusted according to fasting SMPG values documented in the patient diary ([Section 8.1.4](#)).

Patients randomized in the GLP-1 RA arm continue their treatment during the open-label randomized period as before the randomization.

10.1.2.1 Baseline visit (V3, Week 0 and Day 1)

For the complete list and contents of procedures/assessments scheduled for the baseline visit, please refer to the “Study Flow Chart” in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The details of the procedures/assessments to be performed at this visit and which are not described elsewhere are provided below:

At this visit, the patient must return to the investigation site in the morning after 8 hours fasting not having administered GLP-1 RA nor background therapy at home. Patients will visit the site with their blood glucometer and diary.

Note: Patients who are taking a once weekly formulation of GLP-1 RA (Bydureon®, Tanzeum®, or Trulicity®) must have their baseline visit scheduled **at least 1 week** after administering their last dose. If a patient arrives for their baseline visit and is found to have administered their last dose of a once weekly GLP-1 RA less than 1 week prior, the visit should be cancelled and rescheduled to occur at least 1 week after their last dose, but within the allowed window of the screening period as per [Section 10.1.1](#).

Compliance check

Compliance check includes compliance to background OAD treatment and use of glucometer, review of fasting SMPG values, and the 7-point SMPG profile and patient diary. If patient is not appropriately compliant with the study procedures, the training will be repeated by the site staff.

IRT contact

After the baseline assessments are completed and eligibility confirmed, the Investigator contacts IRT for randomization to the study.

The HbA1c will be entered in the IRT (directly by the laboratory or by the Investigator):

If the patient’s HbA1c at the screening (V1) results are $7\% \leq \text{HbA1c} \leq 9\%$, the treatment group (ie, FRC, GLP-1 RA arm) will be notified by IRT.

Training on self-injection devices and dispensation of IMP

Patients randomized to the FRC group are instructed by the study staff how to properly use the combination Peach Pen and Olive Pen as well as how to store it. Instructions on self-injection technique are also given. Injection pen device with the instruction leaflet is dispensed. Please refer to [Section 8.1.2.2](#).

Patients randomized to the GLP-1 RA group are instructed to continue their treatment as before the randomization. Please refer to [Section 8.1.3](#).

Starting dose and dose adjustment of IMP

Eligible patients will enter a 26-week open-label randomized treatment period to receive either FRC or continue GLP-1 RA (Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity®) (see details in [Section 8.1.4](#)).

For patients in the control arm, an appointment for one week later is given to the patient for the next phone call visit. For patients in the FRC arms, an appointment is given for 3-4 days later for the first titration phone call visit (see [Section 10.1.2.4](#)).

A patient card, including emergency contact details will be provided to every patient who participates in the study.

10.1.2.2 Phone call visits: V5 (Week 1); V9 (Week 3); V13 (Week 5); V15 (Week 6); V17 (Week 7); V20 (Week 10); V22 (Week 14); V23 (Week 16); V25 (Week 20); V27 (Week 24)

The patient is called by the Investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the Investigator, the Investigator has to be consulted if AE/SAE is suspected and informed in case AE/SAE occurred. In case of an AE the patient may be asked to come to the investigational site, as appropriate. A phone call visit can optionally be performed as a clinical visit in case of symptomatic hypoglycemia/AE or other reasons.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any hypoglycemic events or symptoms?
- Did you experience any possible allergic symptoms, or skin reactions?
- Do you feel comfortable in handling the diary, glucose meter and IMP injection device or do you need any more explanation?
- Did you adjust IMP since last visit (if appropriate)? What is your IMP dose?
- Which pen you are using? What is the daily dose you are using? Did you adjust IMP since last phone call/visit? In case the patient has used two pens (a peach pen and an olive pen), it should be reported and documented in the diary as well as the doses administered.
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?

- Did you miss, change, take or add any new medications (including OAD if appropriate) since the last visit?
- Did you measure any fasting SMPG value outside of the range 80 to 100 mg/dL (4.4 to 5.6 mmol/L) (patients in the insulin glargine/lixisenatide combination)?

The phone visits will also include:

- Asking patient's fasting pre-breakfast SMPG and the insulin glargine/lixisenatide combination dose on the last 3 measurements including day of visit; (patients in the insulin glargine/lixisenatide combination);
- Adjustment of the dose of IMP (insulin glargine/lixisenatide combination), to continue treatment toward the target fasting SMPG between 80 and 100 mg/dL (4.4 and 5.6 mmol/L), inclusive;
- Recording of AE and symptomatic hypoglycemia events (if any);
- Recording of the use or change of any concomitant medication.

The patient will be instructed to:

- Perform required SMPG measurements;
- Complete the diary;
- Self-inject once daily, twice daily (only for Byetta®), or once weekly (for Bydureon®, Tanzeum®, and Trulicity®) IMP at the dose prescribed by the Investigator;
- Contact the site in case of occurrence of an adverse event, record the event in the patient's diary and return to the site as deemed appropriate.

Give an appointment to the patient for subsequent visits (on-site visit or phone call visit) and remind them to come fasting if planned at next on-site visit.

10.1.2.3 On-Site visits: V7 (Week 2); V11 (Week 4); V19 (Week 8); V21 (Week 12); V24 (Week 18); V26 (Week 22); V28 (Week 26)

For the complete list and contents of procedures/assessments scheduled for the open-label treatment period, please refer to the "Study Flow Chart" in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

For on-site visits, the Investigator or qualified designee contacts IRT treatments in order to allocate the IMP for the patient.

As the patients return their unused kits on these visits, the Investigators or qualified designee will enter in the IRT the quantity of kit(s) unused, and the IRT will take in account this data in order to define the quantity of kits to be allocated.

The details of the procedures/assessments to be performed at visits and which are not described elsewhere are provided bellow.

Compliance check

Compliance check includes compliance to IMP and background OADs treatment and use of glucometer, review of fasting SMPG values, and the 7-point SMPG profile and patient diary.

For all on-site visits patients are instructed to return to the site in the morning in fasting condition with the glucose meter, the diary, and the used /in-use pens. For the on-site visits where a resupply is planned, patients will also bring the unused pens. If patient is not compliant to the study, the training has to be repeated by the site staff.

Upon completion of each on-site visit, an appointment for the next visit (on-site visit or Phone call visit) will be made.

10.1.2.4 Additional titration phone call visits: V4 (Week 0.5), V6 (Week 1.5), V8 (Week 2.5), V10 (Week 3.5), V12 (Week 4.5), V14 (Week 5.5), V16 (Week 6.5) and V18 (Week 7.5)

Twice weekly titrations are recommended as far as possible during the first 8 weeks of treatment in the LixiLan arms (please see [Section 8.1.4.1](#)). Titrations will be done at the scheduled weekly visits (V5, V7, V9, V11, V13, V15, V17, V19) plus at one additional weekly titration phone call visit to be scheduled between the weekly visits (V4, V6, V8, V10, V12, V14, V16, V18). The additional titration phone call visit should be scheduled to allow for at least two days in between successive visits (example: weekly visits to occur on Mondays and titration phone calls to occur on Thursdays or Fridays). In case the additional phone call is missed during the week, the titration should continue as per the originally planned schedule. These additional phone calls are only for titration purposes, and recommendations should be based on the SMPG measurements and IMP dose administered.

The following 2 questions will be asked to the patient:

- Did you experience any new medical event, disease, or symptom since the last visit?
- Did you experience any hypoglycemic events or symptoms?

If the answer is yes to any of these questions, the adverse event or hypoglycemic event is to be reported, and it needs to be taken into account for the titration recommendation.

10.1.2.5 Final on-treatment assessment/end of treatment visit for randomized treatment period (V28, Week 26)

For the complete list and contents of procedures/assessments scheduled for the open-label treatment period, please refer to the “Study Flow Chart” in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The same procedures/assessments including IRT contact as planned at V28 (Week 26) have to be performed in case of prematurely permanent treatment discontinuation ([Section 10.3.2](#)). The IRT has to be contacted in order to register the end of randomized treatment period for patients not eligible to the extension period.

At V28 (Week 26) an appointment for the post-treatment follow-up phone call visit will be made for patients not eligible to the extension period.

10.1.2.6 Post-treatment follow-up phone call visit for randomized treatment period

Post-treatment follow-up phone call visit is performed 3 (-1/+3) days following the last injection of the IMP (or 9 (-1/+3) days for patients receiving weekly GLP-1 RA). The visit is performed both for patients who completed the study and patients who withdrew from the study at the time of IMP discontinuation. The visit is NOT performed for patients who prematurely discontinued the IMP treatment and stay in the study. For patients continuing in the extension period, the visit is not performed in the randomized treatment period. This visit can be a phone call visit, or an on-site visit in case of ongoing or new adverse event during the post-treatment period, if necessary.

The patient is called by the Investigator or medically qualified designee at a certain, previously agreed time point.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you change, take or add any new medications since the last visit?
- Did you experience any hypoglycemic symptoms or events?

All reports of hypoglycemic events (if any) or any adverse events are recorded. The use or change of any concomitant medications, including rescue therapy, is recorded.

IRT is contacted for notification of the end of study.

10.1.3 Extension period (Week 26 to Week 52)

Patients meeting all inclusion criteria in the FRC treatment group and with no exclusion criteria at the end of the randomized treatment period V28 (Week 26) continue into the extension period. The duration of the extension period for all patients is 26 weeks \pm 5 days from end of the randomized treatment period visit (V28, Week 26) to the end of the extension visit (V35, Week 52).

10.1.3.1 Baseline visit for the extension period: V28a (Week 26)

V28a is performed on the same day as V28, upon completion of V28 procedures for patients consenting for the extension period.

Eligibility for the extension will be assessed for patients treated with the FRC. Eligible patients will continue to use the FRC for the next 26 weeks of the extension period.

The investigator will contact the IRT in order to allocate the IMP for patients who will continue in the extension period. Diary and IMP will be dispensed.

10.1.3.2 The investigator will contact the IRT in order to allocate the IMP for patients who will continue in the extension period. Diary and IMP will be dispensed. Phone call visits: V29 (Week 30); V31 (Week 38); V33 (Week 46); V34 (Week 50)

The patient is called by the Investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the Investigator, the Investigator has to be consulted if AE/SAE is suspected and informed in case AE/SAE occurred. In case of an AE the patient may be asked to come to the investigational site, as appropriate. A phone call visit can optionally be performed as a clinical visit in case of symptomatic hypoglycemia/AE or other reasons.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any hypoglycemic events or symptoms?
- Did you experience any possible allergic symptoms, or skin reactions?
- Do you feel comfortable in handling the diary, glucose meter and IMP injection device or do you need any more explanation?
- Did you adjust IMP since last visit (if appropriate)? What is your IMP dose?
- Which pen you are using? What is the daily dose you are using? Did you adjust IMP since last phone call/visit? In case the patient has used two pens (a peach pen and an olive pen), it should be reported and documented in the diary as well as the doses administrated.
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you miss, change, take or add any new medications (including OAD if appropriate) since the last visit?
- Did you measure any fasting SMPG value outside of the range 80 to 100 mg/dL (4.4 to 5.6 mmol/L)?

The phone visits will also include:

- Asking patient's fasting pre-breakfast SMPG and the insulin glargine/lixisenatide combination dose on the last 3 measurements including day of visit;
- Adjustment of the dose of IMP, to continue treatment toward the target fasting SMPG between 80 and 100 mg/dL (4.4 and 5.6 mmol/L), inclusive;
- Recording of AE and symptomatic hypoglycemia events (if any);
- Recording of the use or change of any concomitant medication.

The patient will be instructed to:

- Perform required SMPG measurements;
- Complete the diary;
- Self-inject once daily IMP at the dose prescribed by the Investigator;

- Contact the site in case of occurrence of an adverse event, record the event in the patient's diary and return to the site as deemed appropriate;
- Give an appointment to the patient for subsequent visits (on-site visit or phone call visit) and remind them to come fasting if planned at next on-site visit.

10.1.3.3 On-Site visits: 30 (Week 34); V32 (Week 42)

For the complete list and contents of procedures/assessments scheduled for the open-label treatment period, please refer to the "Study Flow Chart" in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

For on-site visits, the Investigator or qualified designee contacts IRT treatments in order to allocate the IMP for the patient.

As the patients return their unused kits on these visits, the Investigators or qualified designee will enter in the IRT the quantity of kit(s) unused, and the IRT will take in account this data in order to define the quantity of kits to be allocated.

The details of the procedures/assessments to be performed at visits and which are not described elsewhere are provided below.

Compliance check

Compliance check includes compliance to IMP and background OADs treatment and use of glucometer, review of fasting SMPG values, and patient diary.

For all on-site visits patients are instructed to return to the site in the morning in fasting condition with the glucose meter, the diary, and the used /in-use pens. For the on-site visits where a resupply is planned, patients will also bring the unused pens. If patient is not compliant to the study, the training has to be repeated by the site staff.

Upon completion of each on-site visit, an appointment for the next visit (on-site visit or Phone call visit) will be made.

10.1.3.4 Final on-treatment assessment/end of treatment for the extension period visit (V35, Week 52)

For the complete list and contents of procedures/assessments scheduled for the open-label treatment period, please refer to the "Study Flow Chart" in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The same procedures/assessments including IRT contact as planned at V28 (Week 26) have to be performed either at V35 or in case of prematurely permanent treatment discontinuation ([Section 10.3.2](#)). The IRT has to be contacted in order to register the end of treatment.

At V35 (Week 52) an appointment for the post-treatment follow-up phone call visit will be made.

10.1.3.5 Post-treatment follow-up phone call visit for the extension period visit

Post-treatment follow-up phone call visit is performed 3 (-1/+3) days following the last injection of the IMP. The visit is performed both for patients who completed the extension period and patients who withdrew from the extension period at the time of IMP discontinuation. The visit is NOT performed for patients who prematurely discontinued the IMP treatment and stay in the study.

This visit can be a phone call visit, or an on-site visit in case of ongoing or new adverse event during the post-treatment period, if necessary.

The patient is called by the Investigator or medically qualified designee at a certain, previously agreed time point.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you change, take or add any new medications since the last visit?
- Did you experience any hypoglycemic symptoms or events?

All reports of hypoglycemic events (if any) or any adverse events are recorded. The use or change of any concomitant medications, including rescue therapy, is recorded.

IRT is contacted for notification of the end of study.

10.1.4 Unscheduled phone call

In case that an unscheduled telephone visit during the treatment period occurs, the following information should be asked for:

- During the phone call, ask the patient:
 - Did you experience any new medical event, disease or symptom since the last visit? (Please pay attention to any possible hypoglycemic event or symptom, possible allergic or injection site reactions).
 - Did you experience any change in a pre-existing medical event or disease or symptom since the last visit?
 - Did you change or add any concomitant medication since the last visit?
 - Did you have any technical difficulties with use of the glucometer?
- Review with the patient:
 - Diet and lifestyle counseling.

- Instruct patients by:
 - Providing information on how to adjust dose according to their SMPG values;
 - Encourage patients to continue to measure required SMPGs in the Sponsor provided glucometer and complete the insulin doses and hypoglycemic form in the diary for all hypoglycemic events.
- Record in the clinical database:
 - Any changes to concomitant medication;
 - AE/SAE, injection site reaction, allergic reaction, and hypoglycemia if any;
 - Any fasting SMPG leading to titration of the FRC dose in the interim since the last visit (3 fasting SMPG measurements for each dose adjustment), which is entered into the clinical database.
- Other SMPG and FRC doses for these telephone visits related to usual care may be reviewed in the glucometer and patient diary and are not transferred into the clinical database unless there has been titration of basal insulin or hypoglycemia.

Patient is called by the Investigator or qualified designee at a scheduled time. Patient may at the discretion of the Investigator, communicate SMPG and AE/SAE via email or fax, which is then, placed into the source documents.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in the patient's file

Evaluations that are reported in the e-CRF must be supported by appropriately signed identified source documentation related but not limited to the following:

- Agreement and signature of informed consent mentioning the study identification;
- Patient identification, last participation in a clinical trial (if any), medical history, associated diseases, and data related to the studied pathology;
- Contraception method(s) for women of childbearing potential;
- Reason for lack of childbearing potential for concerned women (eg, postmenopausal, history of hysterectomy);
- Previous and concomitant medication (including background OADs and rescue therapy);
- Study identification;
- Treatment kit number, dates of administration and doses of FRC or GLP-1 RA (Peach pen, Olive pen, Victoza®, Byetta®, Bydureon®, Tanzeum®, or Trulicity® injectors);
- Compliance to metformin and pioglitazone (if applicable) and SGLT2 inhibitors (if applicable) assessed by interview and patient's diary;
- Dates of visits and assessments including the examination report;
- Vital signs, height, body weight;

- Printed or faxed central lab reports received at site (dated and signed by the Principal Investigator or Sub-Investigator);
- IRT confirmation notifications by fax or e-mail (screening, screen failure, randomization, treatment reallocation, treatment/study discontinuation, end of study treatment replacement if applicable, etc);
- ECG records signed and dated;
- Adverse events and follow-up;
- In case of SAE or AEs requiring specific monitoring, eg, increased lipase/amylase >2 x ULN, increased calcitonin, the site should file in the source document at least copies of the hospitalization reports if applicable and any relevant examination reports (eg, imaging reports, specialists' reports...) documenting the follow-up of the SAE or the specific AE;
- Date of premature study discontinuation (if any) and reason.

Source documentation may be found in the following:

- Patient's identity;
- Medical history;
- Nursing notes;
- Dietician's notes;
- Physician's notes;
- Patient's diaries;
- Dated and signed print-outs with SMPG downloaded from glucose meter.

10.2.2 Source data verification requirements for patients not randomized

For patients not randomized, the source data that must be checked include the patient's identification details, the informed consent signed by the patient, the study identification, the dates of study visits and the main reasons preventing randomization.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs or for other reasons. In case of treatment interruption due to an AE, reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the

responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to [Section 7.1](#) and [Section 7.2](#)).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients may withdraw from treatment with IMP in case of the following reasons:

- At patient's own request, ie, withdrawal of consent for treatment;
- If, in the Investigator's opinion, continuation with the administration of IMP would be detrimental to the patient's well-being;
- At the specific request of the Sponsor.

A patient must withdraw from treatment with IMP in case of the following:

- Intercurrent condition that requires discontinuation of IMP: eg, laboratory abnormalities (see decision tree and general guidance for the follow up of laboratory abnormalities in [Appendix B](#)), diagnosis of acute pancreatitis confirmed by gastroenterologic evaluation and imaging (see [Section 10.6.4](#)) calcitonin value ≥ 50 pg/mL (see [Section 10.6.5](#));
- Pregnancy.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (eg, after 24 hours) before making a decision of permanent discontinuation of the IMP for the patient concerned.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be maintained in the study as much as possible and followed-up according to the study procedures as specified in this protocol (except for the 3 day safety post-treatment follow-up assessment) up to the scheduled date of study completion, or up to recovery or stabilization of any AE requiring follow-up as specified in this protocol, whichever comes last.

If possible, after the permanent discontinuation of treatment regardless of the reason, the patients will be assessed as soon as possible using the procedure normally planned for the last dosing day

with the IMP (V28/End of randomized treatment visit for patients who discontinued the IMP before V28 (Week 26), or V35/end of extension treatment visit for patients who entered the extension period and discontinued the FRC before V35 (Week 52)).

For the meal test, please refer to [Section 9.2.1.2.2](#).

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF and in the patient's medical records when considered as confirmed. IRT should be notified when a patient prematurely discontinues treatment.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All cases of study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented. IRT should be notified when a patient withdraws from the study.

For patients who fail to return to the site, unless the patient withdraws the consent for follow-up, the Investigator should make the best effort to re-contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm,
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia),
 - Convulsions (seizures, epilepsy, epileptic fit, absence seizures, etc).
- Development of drug dependence or drug abuse,
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),

- Bullous cutaneous eruptions,
- Cancers diagnosed during the study or aggravated during the study,
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

All AESI will be reported to the Sponsor in the same timeframe as SAEs, ie within 24 hours as detailed in [Section 10.4.1.2](#).

AESI are listed below:

- Confirmed ALT increase ($>3 \times$ ULN) (see [Appendix B](#));
- Pregnancy occurring in a female patient entered in the study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP;
 - Pregnancy will be recorded as an AESI with immediate notification in all cases.
 - It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#));
 - In the event of pregnancy in a female participant, IMP should be discontinued;
 - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or non-serious) with IMP/NIMP

An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systemic pen counts) and defined as follows:

- For insulin glargine/lixisenatide combination: any dose corresponding to a lixisenatide daily dose greater than 40 μ g (ie, >80 U for Peach pen and >120 U for Olive pen);
- For GLP-1 RA: any dose greater than 2-fold above the recommended/planned or prescribed dose administered per day within this Clinical Trial (ie, greater than 3.6 mg per day for Victoza®, greater than 40 μ g per day for Byetta®, greater than 4 mg per week for Bydureon®, greater than 100 mg per week for Tanzeum®, and greater than 3 mg per week for Trulicity®);
- For background OADs, any dose greater than 2-fold above the recommended/planned or prescribed dose administered per day within this Clinical trial.

The circumstances of the overdose (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

Note: Asymptomatic overdose with IMP does not need immediate notification, and thus is to be reported in the standard AE pages in the e-CRF.

10.4.1.4 AEs requiring specific monitoring and reporting on specific e-CRFs

The following AEs require specific monitoring and should be reported on the specific e-CRF for completion. These AEs will only qualify for expedited reporting when Serious (fulfilling SAE criteria).

- Suspected allergic reactions (please refer to [Section 10.6.3](#));
- Monitoring of patients with increased pancreatic enzymes $>2 \times$ ULN/pancreatic events (please refer to [Section 10.6.4](#));
- Monitoring of patients with increased calcitonin ≥ 20 pg/ mL (please refer to [Section 10.6.5](#));
- Monitoring of device-related events (please refer to [Section 10.6.8](#)).

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or;
 - Requiring either corrective treatment or consultation, and/or;
 - Leading to IMP discontinuation or modification of dosing, and/or;
 - Fulfilling a seriousness criterion, and/or;
 - Defined as an AESI or event requiring specific monitoring.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work (please see [Appendix C](#)).

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.1.3](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

Instructions for AE reporting are summarized in [Table 2](#).

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix B](#).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia;
- Thrombocytopenia;
- Increase in ALT;
- Acute renal insufficiency;
- Suspicion of rhabdomyolysis.

Table 2 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety complementary form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy of female patient	Yes	No	Yes
		Pregnancy of female partner of male patient	Yes	No	Yes
		Symptomatic overdose* with IMP/NIMP	Yes	Yes	No
		Confirmed increase in ALT >3x ULN	Yes	No	Yes
AEs requiring specific monitoring (non-SAEs)	Routine	Suspected allergic reactions	Yes	No	Yes
		Confirmed increase amylase/lipase >2x ULN	Yes	No	Yes
		Confirmed increased calcitonin ≥ 20 pg/mL	Yes	No	Yes
		Device-related events#	Yes	No	Yes
Laboratory, vital signs, ECG abnormality asymptomatic overdose recorded as AE (non-SAE, non-AESI)	Routine	Neutropenia	Yes	No	No
		Thrombocytopenia	Yes	No	No
		Acute renal insufficiency	Yes	No	No
		Suspicion of rhabdomyolysis	Yes	No	No
		Other (eg, leading to IMP discontinuation)	Yes	No	No

Symptomatic hypoglycemia will be reported on the dedicated hypoglycemia event page.

*: Asymptomatic overdose is reported in the AE form and does not require expedited reporting.

#: Only device-related events associated with clinical adverse events will be reported as AE. Please refer to [Section 10.6.8](#).

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Any other AE not listed as an expected event in the lixisenatide/insulin glargine combination product Investigator's Brochure (IB) or the approved labelling referenced in [Section 16](#), ie, EU SmPC for Victoza®, Byetta®, Bydureon®, or Trulicity® or US Prescribing Information for Tanzeum®-will be considered as an unexpected event.

In this study, some AEs considered related to the underlying condition (eg, blood glucose increased) will not be considered unexpected as given in the IB or the approved labelling referenced in the protocol.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report (CSR).

10.6 SAFETY INSTRUCTIONS

10.6.1 Symptomatic Hypoglycemia

Symptomatic hypoglycemia events will be categorized as follows:

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.

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.

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 improved with oral carbohydrate, or Intravenous glucose or glucagon injection without a test of plasma glucose.

Patients will be instructed to measure finger-stick plasma glucose levels prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose administration prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation. Details on hypoglycemia episodes will be captured in the patient diaries, and patients will contact the sites as soon as possible following severe events to review the details and decide on any necessary measures to be taken.

Symptomatic hypoglycemia episodes will be documented on the dedicated hypoglycemia event page in the e-CRF. Symptomatic hypoglycemia events fulfilling the criteria of a SAE will also be documented on AE and SAE forms in the e-CRF.

10.6.2 Local tolerability at injection site

In case the Investigator or the patient recognizes any signs of local intolerance at injection site this should be recorded on the standard AE page in the e-CRF.

10.6.3 Allergic or allergic-like reaction

In case a patient experiences an allergic reaction or an allergic-like reaction this has to be reported as an adverse event and recorded in the e-CRF on the specific AE form for suspected allergic event. Additional information is collected on specific allergic reaction complementary form. Allergic reaction or possible allergic reaction will be adjudicated by the ARAC ([Section 6.4.2](#)).

Virtually all symptoms listed on the allergic reaction complementary form are possible adverse reactions that may be allergic in nature and may need to be addressed after medical judgment, excluding another etiology than allergy.

Sometimes transient injection site reactions, irritant in nature, may occur requiring no intervention and are of dubious significance. These reactions would not be considered to be allergic reactions. Adverse events that are obviously not of allergic origin (eg, local injection site reactions) should not be recorded on the Allergic Event page or Allergic Reaction Complementary Form.

10.6.4 Monitoring of patients with increased lipase and/or amylase >2x ULN

Potential safety signals for acute pancreatitis have been identified in the post-marketing experience of other GLP-1 receptor agonists. Therefore, patients enrolled in this study should be followed for any suspected pancreatitis, eg, with symptoms and/or signs of acute abdominal distress or abnormal levels of pancreatic enzymes. Serum amylase and lipase concentrations are monitored routinely at screening, baseline and periodically during the study treatment period.

In the presence of clinical signs and/or symptoms evocative of pancreatitis, eg, persistent abdominal pain, which can radiate to the back, often with characteristic positional features, with possible occurrence of nausea, vomiting, fever and leukocytosis, further measurement of amylase and lipase should be performed. The clinical signs and/or symptoms should be documented in the source data.

(1) Elevation of Amylase and/or Lipase >2x ULN without clinical signs and/or symptoms

In any case where amylase and/or lipase are >2x ULN, a retest (centrally assessed as far as possible) must be performed as follows:

- If value(s) is/are >2-3x ULN: retest within 7 days;
- If value(s) is/are >3x ULN: retest within 48 hours;
- If the value(s) remain(s) >2x ULN upon retesting: amylase and/or lipase levels should be retested weekly until values are <2x ULN.

In case a retest is >2x ULN a gastroenterological evaluation and imaging (ultrasound and/or CT or MRI with contrast, as appropriate) must be performed. Please document in the source data the absence of clinical signs and/or symptoms (if clinical signs and/or symptoms develop, please see part (2) below).

Best clinical judgment is to be used when interpreting elevated serum amylase and lipase levels in asymptomatic patients. Temporary discontinuation of the IMP may be considered in these cases if deemed necessary by the Investigator.

(2) Elevation of Amylase and/or Lipase >2 x ULN with clinical signs and/or symptoms

In the presence of clinical signs and/or symptoms evocative of pancreatitis (as described above) associated with elevated amylase and/or lipase, treatment with the IMP should be promptly and at least temporarily discontinued pending further clinical evaluation and diagnosis confirmation.

Clinical signs and/or symptoms are to be documented in the source data. A laboratory determination of amylase and lipase has to be obtained at the time of the event and again within 48 hours or earlier as clinically indicated. If the value(s) remain(s) >2x ULN, then amylase and/or lipase levels should be retested as described in (1) above, or more often if clinically indicated.

A gastroenterologic evaluation and imaging (ultrasound and/or CT or MRI with contrast, as appropriate) must be performed. If a diagnosis of pancreatitis is confirmed, IMP should not be restarted and should be permanently discontinued.

In both cases as described above under (1) and (2), all laboratory or clinical documentations are to be collected. If the retest confirms lipase and/or amylase values are >2x ULN, the event must be reported in the e-CRF on the specific AE form for “Increased Lipase and/or Amylase >2x ULN” and the specific forms, using the appropriate verbatim: eg, “increased amylase and/or lipase” in case of isolated enzyme elevation, “suspected pancreatitis” in the presence of clinical signs evocative of pancreatitis if the diagnosis is suspected but cannot be confirmed or excluded, and “pancreatitis” if the diagnosis has been confirmed.

The PSAC will review selected pancreatic events, including pancreatitis, pancreatic neoplasms and abnormal levels of amylase or lipase.

10.6.5 Management of patients with increased calcitonin values

During the course of the study, if a calcitonin value is found ≥ 20 pg/mL (5.9 pmol/L):

- A retest should be performed by the central laboratory within 7 days. In addition, blood should be collected and sent to the central laboratory for measurement of: calcium, phosphorus, gastrin, Thyroid Stimulating Hormone (TSH), and anti-thyroid peroxidase (anti-TPO) antibodies;
- The clinical and laboratory documentations listed below are to be collected and recorded in source documents as soon as possible:
 - Potential false positive circumstances: smoking status, proton-pump inhibitor treatments (eg, omeprazole), autoimmune thyroid diseases (Hashimoto's thyroiditis or Graves' disease), differentiated thyroid cancer, hypercalcemia, hypergastrinemia, chronic renal insufficiency (not on dialysis), other neuro-endocrine tumors (small cell lung cancer, intestinal carcinoid), acute pulmonary inflammatory conditions, or sepsis.
 - Specific personal and/or familial medical history in relation to thyroid or other endocrine diseases;
 - Specific physical examination (neck, thyroid gland).

If the retest confirms that the calcitonin value is ≥ 20 pg/mL:

- The event must be reported in the e-CRF on the specific AE form and specific complementary form for "increased calcitonin ≥ 20 pg/mL" with all appropriate clinical and laboratory documentation.
- An ultrasound scan of the thyroid should be performed and the patient may be referred to a thyroid specialist if judged necessary.
- The patient should continue to be followed according to protocol schedule (including planned calcitonin measurements). The specific AE form "increased calcitonin ≥ 20 pg/mL (5.9 pmol/L)" should be updated with any new information collected during the follow up.
- If a calcitonin value ≥ 50 pg/mL (14.75 pmol/L) is found at any time during further follow up, the patient should be permanently discontinued from IMP (see [Section 10.3.4](#)) and referred to a specialist. As far as possible, blood should be collected 1 to 2 weeks after IMP discontinuation and sent to the central laboratory for calcitonin measurement.
- If at any time during follow-up a calcitonin value ≥ 20 pg/mL increases by 20% or more between 2 assessments (while remaining below 50 pg/mL), a repeated measurement should be performed earlier than scheduled in the protocol, ie, 1 month later. Once results are available, discussion with Sponsor should be initiated without delay for further guidance.

10.6.6 Monitoring of renal function in case of prolonged and severe nausea and vomiting

In case of prolonged or severe nausea and vomiting, if clinically indicated, serum creatinine measurement has to be centrally performed. If there is an acute increase of serum creatinine, metformin has to be discontinued until resolution of renal dysfunction.

10.6.7 Follow-up of laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities are provided in [Appendix B](#).

10.6.8 Monitoring of device-related events

A device-related event (DRE) includes any suspected problem with the injection device(s) used in the study which has or may lead to a health hazard (eg, adverse event). Typical problems include pen performance failure, patient (or caregiver) having difficulty understanding the instructions or using the pen or auto-injector, use error, etc.

Examples of device-related events include but are not limited to:

- Dosing problems: jamming, inability to inject, partial injection, need to repeat injection, dosage knob stuck;
- Needle issues: difficulty attaching the needle;
- Breakage of the pen;
- Mix-up of pens/devices (patient injects using a pen/device different than the intended one);
- Difficulty to understand the instructions in the product instructions leaflet;
- Use error: Incorrect use of the pen/device by the patient/caregiver/healthcare provider.

Device-related events will be pro-actively monitored during the study by asking at each study visit whether the patient/caregiver experienced any DRE. If answer is yes, the specific e-CRF Device-Related Event Questionnaire (DREQ) will be completed.

If the device-related event is associated with a symptomatic hypoglycemic event, a hyperglycemic adverse event or another adverse event, the corresponding symptomatic hypoglycemic forms or adverse event forms must also be completed. This associated adverse event will be qualified as a serious adverse event only if it fulfills seriousness criteria, and in this case, the SAE reporting procedure (see [Section 10.4.3](#), Instructions for reporting serious adverse events) should be followed.

As needed, further instruction and troubleshooting guidance should be provided to the patient by the study site according to the instructional materials/troubleshooting guide provided by the Sponsor.

For device-related events, related to Solostar Pen for patients on FRC, that are not resolved by further guidance/review of instructions or troubleshooting with the pen during the visit (on site visit or phone visit), a PTC form must be completed, the pen associated with the event should be

retrieved, and both should be sent to the manufacturing site for technical investigation and determination of the root cause.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable change in HbA1c from baseline to Week 26 and intent-to-treat (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 FRC dropped patients are assumed to respond the same as the control patients, ie, no treatment difference between the FRC dropped patients 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.

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented in the CSR:

- Screened patients: patients who have signed the informed consent;
- Randomized patients: patients with a treatment kit number allocated and recorded in IRT database, and regardless of whether the treatment kit was used or not;
- The modified intent-to-treat (mITT) population (as defined in [Section 11.3.1.1](#) and analyzed as randomized);
- The safety population (ie, randomized and treated patients);
- The pharmacokinetic (PK) population (as defined in [Section 11.3.3](#));
- The randomization strata [HbA1c at visit 1 (<8%, ≥8%) and GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening assigned by IRT will be summarized. The discrepancy between the strata assigned by IRT and the information reported on electronic Case Report Form (e-CRF) will be listed for all randomized patients;
- Patients who have completed the 26-week randomized treatment period;
- Patients who have completed the whole study treatment period including 26-week extension period;
- Patients who discontinued the IMP during the 26-week randomized treatment period, and the reasons for treatment discontinuation.
- Patients who discontinued the IMP during the whole study treatment period, and the reasons for treatment discontinuation.

For all categories of patients except screened patients, percentages will be calculated using the number of randomized patients as denominator for each treatment group.

A list of patients prematurely discontinued from the treatment, along with reasons for discontinuation, will be provided.

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.

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.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Efficacy analyses will be based on the treatment group allocated by the IRT according to the randomization schedule at randomization visit (as randomized), irrespective of the treatment actually received.

11.3.1.1 Modified intent-to-treat population

Efficacy analyses will be based on the mITT population, defined as all randomized patients who have both a baseline assessment and at least one 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.

11.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least one 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, but their safety data will be presented separately;
- Randomized patients for whom it is unclear whether they took the study medication 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 was 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.

11.3.3 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.

11.4 STATISTICAL METHODS

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

Categorical data will be summarized by treatment group using count and percentage.

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

11.4.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the first dose of open-label Investigational Medicinal Product (IMP). Derived parameters will be computed by the sponsor.

Demographic characteristics to be summarized are:

- Age (years) derived as: $(\text{Date of informed consent} - \text{Date of birth})/365.25$;
- Age categories (<50 , ≥ 50 to <65 , ≥ 65 to <75 , ≥ 75 years of age);
- Gender (Male, Female);
- Race;
- Ethnicity (Hispanic, Not Hispanic);
- HbA1c (%) at V1(Week -2);
- Baseline BMI (kg/m^2) derived as: $(\text{Weight in kg})/(\text{Height in meters})^2$;
- Baseline BMI level (<30 , ≥ 30 kg/m^2);
- Randomization strata of HbA1c (<8 , $\geq 8\%$) at screening visit 1 (V1, Week -2);
- Randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening;
- Country.

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 [once/twice daily formulations (Victoza® or Byetta®), once weekly 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);
- 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);
- 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);
- 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 sensory or motor neuropathy, diabetic autonomic 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) /1.73m²;
- eGFR categories at screening (<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]).

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) 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.

- 7-point (average and each time point) SMPG;
- Body weight;
- Fasting plasma glucose (by central laboratory).

Medical history and medical findings include:

- Medical or surgical history (including physical examination abnormalities);
- Medical history of cardiovascular and cerebrovascular events;
- Medical history of allergies;
- Subject family allergy history;
- Alcohol habits within the last 12 months;
- Smoking habits.

Medical and surgical history will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock. Medical history of cardiovascular and cerebrovascular events and medical history of allergies will be summarized by searching for relevant “preferred term (PT)” identified by medical and coding teams.

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 will be summarized with appropriate descriptive statistics. Pathologies associated with past medical or surgical history will be summarized by primary system organ class (SOC) and high level term (HLT). These summaries will be provided on randomized patients for each treatment group (and overall).

11.4.2 Prior and concomitant medications

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 three groups:

- Prior medications are those the patient took prior to the first injection of open-label IMP;
- Concomitant medications are those the patient continued or started on or after the first dose 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. Medications will be summarized according to the WHO-DD, considering the first digit of the ATC class (anatomic category) and the first three digits of the ATC class (therapeutic category). 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 time for the same medication.

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.

11.4.3 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received in the safety population.

11.4.3.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed by the duration of treatment exposure during the study.

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

The duration of daily IMP exposure will be calculated as:

$(\text{Date of the last open-label IMP injection} - \text{Date of the first open-label IMP injection}) + 1.$

The duration of weekly IMP exposure will be calculated as:

$(\text{Date of the last open-label IMP injection} - \text{Date of the first open-label IMP injection}) + 7.$

The number (%) of patients randomized and exposed to the open-label IMP will be presented by specific time periods for each treatment group in the safety population. The time periods of interest are grouped as follows:

- 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.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in patient year will also be presented by treatment group in the safety population.

11.4.3.2 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 once/twice daily formulation

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

For once weekly formulations,

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

11.4.4 Analyses of efficacy endpoints

Efficacy analyses will be performed on the mITT population using efficacy assessment obtained 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 measurement for that endpoint.

11.4.4.1 Analysis of primary efficacy endpoint

See [Section 9.1.1](#).

Primary analysis

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

The primary efficacy endpoint (change in HbA1c 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 HbA1c (<8%, ≥8%) at V1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly 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 HbA1c value-by-visit interaction as the covariates. The adjusted mean change in HbA1c 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 and the 95% confidence interval (CI) for the adjusted mean.

The MMRM model will be implemented using Statistical analysis system (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 HbA1c measurements.

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 9.2](#)).
- 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 medication, the same MMRM model as described in the primary analysis will be performed by excluding the measurements after receiving the rescue medication.
- 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 HbA1c 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 Analysis of covariance (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;
- Ethnicity (Hispanic, Not Hispanic);
- Age group (<50, ≥50 to <65, ≥65 to <75, ≥75 years of age);
- Gender;
- Baseline BMI level (<30, ≥30 kg/m²);
- Baseline GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations);
- Baseline HbA1c (<8%, ≥8%);
- Pioglitazone use (Yes, No) at screening;
- 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 HbA1c in the mITT population, and using the MMRM approach with treatment group (FRC or GLP-1 receptor agonist), randomization strata of HbA1c (<8%, ≥8%) at V1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly 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 HbA1c 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 HbA1c 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), \geq LLOQ to 100 nmol/L, >100 nmol/L.

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.

The change of HbA1c from baseline over time by visit will be evaluated by descriptive statistics (mean, SD, median and ranges) by treatment for the 26-week randomized treatment period and for FRC group for the whole study period including the extension period.

11.4.4.2 Analyses of secondary efficacy endpoints

Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided by treatment for all continuous secondary variables defined in [Section 9.2.1](#) at the scheduled visits for the 26-week randomized treatment period. For continuous variables in the extension period defined in [Section 9.2.1](#), descriptive statistics will be provided for FRC group at the scheduled visits for the whole study period including the extension period.

Except for 2-hour PPG and glucose excursion, all continuous secondary efficacy endpoints at Week 26 defined in [Section 9.2.1](#) will be analyzed using the same MMRM approach as described in [Section 11.4.4.1](#) 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 HbA1c (<8%, \geq 8%) at V1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly 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. The analyses include all scheduled measurements collected during the 26-week randomized treatment period including those obtained after IMP discontinuation or rescue medication use.

2-hour PPG and glucose excursion, for which only one post baseline measurement is scheduled, will be analyzed using the similar ANCOVA with the missing data at Week 26 imputed by LOCF as described in [Section 11.4.4.1](#) 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 HbA1c (<8%, \geq 8%) at V1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, and world region, and a covariate using the corresponding baseline value. Means and adjusted 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 collected during the 26-week randomized treatment period as the value at Week 26.

All categorical secondary efficacy endpoints defined for the 26-week randomized treatment period in [Section 9.2.1](#) will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata of HbA1c (<8%, ≥8%) and randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening visit (V1, Week -2). 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 the categorical secondary endpoints defined for the extension period in [Section 9.2.1](#), counts and percentages will be summarized using all data available at Week 52, with patients having data missing at Week 52 treated as non-responders.

11.4.4.3 Multiplicity considerations

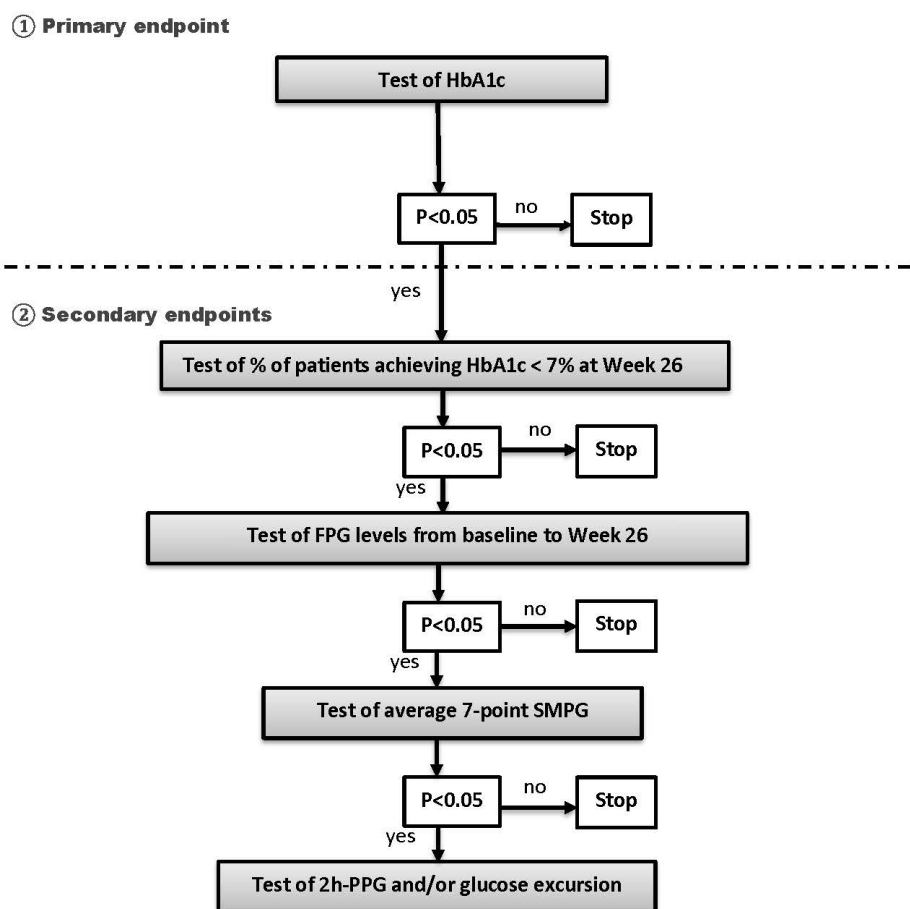
To control the type I error, a step-down testing procedure (please see [Figure 1](#)) will be applied.

For the primary efficacy endpoint (change from baseline to Week 26 in HbA1c), 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 HbA1c <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.

Figure 1 - The step-down testing procedure



11.4.5 Analyses of other endpoints

Analyses of other endpoints defined in [Section 9.3](#) will be performed on the mITT population using all assessments obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy. The similar analyses will also be performed using assessment obtained during 26-week on-treatment period (see [Section 9.2](#)), unless otherwise specified. Descriptive statistics will be summarized by treatment group. For selected other endpoints defined in [Section 9.3.2](#), descriptive statistics will also be summarized for FRC group for the whole study period including the extension period.

For PK parameters, lixisenatide total plasma concentrations 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. The results of the PK evaluation and the immunogenicity assessments will be issued separately from the study report.

11.4.6 Analyses of safety data

See [Section 9.2.2](#).

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

All safety analyses will be performed on the safety population as defined in [Section 11.3.2](#) using the following common rules:

The baseline value is defined as the last available value prior to the first injection of open-label IMP.

The following definitions will be applied to laboratory parameters and vital signs.

- The potentially clinically significant abnormality (PCSA) values for clinical laboratory tests and vital signs are defined as abnormal values considered medically important by Sponsor's Global Pharmacovigilance and Epidemiology department and in effect at the time of the final SAP approval. 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 on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

The "observation period" defined in [Section 9.2.1.1](#) are applicable for classification of symptomatic hypoglycemia, AEs, determination of on-treatment PCSA values and the last on-treatment value for the laboratory, vital sign and ECG parameters.

11.4.6.1 Analyses of symptomatic hypoglycemia

See [Section 10.6.1](#).

The number (%) of patients and event rate in patient years (2 types: the number of patients with events or the total number of events per 100 patient-year) of each type of symptomatic hypoglycemia (severe, documented and probable symptomatic hypoglycemia) will be summarized by treatment group. The pattern of symptomatic hypoglycemia occurrence over time will also be assessed, as appropriate.

11.4.6.2 Analyses of adverse events

Pre-treatment AEs are AEs that developed or worsened or became serious pre-treatment period.

Treatment-emergent AEs (TEAEs) 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 treatments up to 3 days (9 days for the weekly GLP1) after the last administration..

Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

The primary focus of AE reporting in the CSR will be on TEAEs. Pre- and post-treatment AEs will be described separately.

All adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. 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 group.

Summaries of all TEAEs in each treatment group will include:

- The overview of AEs, summarizing number (%) of patients with any
 - TEAE;
 - serious TEAE;
 - TEAE leading to death;
 - TEAE leading to permanent treatment discontinuation;
- The number (n) and percentage (%) of patients with at least one AE by primary SOC, HLGT, HLT and PT;
- Summary of TEAEs by maximal severity (severe, moderate, mild), presented by primary SOC and PT;
- Summary of TEAEs possibly related to open-label IMP, presented by primary SOC and PT.

A detailed listing of TEAE summaries will be provided in the statistical analysis plan.

Death and serious adverse events

Death and treatment-emergent SAEs will be summarized and presented as number and percent of patients in each treatment group.

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) summarized on the safety population by treatment received;
- Death in nonrandomized or randomized and not treated patients;
- TEAE leading to death (death as an outcome on the AE e-CRF 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.

Adverse events leading to permanent treatment discontinuation

TEAEs leading to permanent treatment discontinuation will be summarized and presented as number and percent of patients in each treatment group.

Local tolerability at injection site

AEs related to local intolerability at the injection site will be identified by searching the term “injection site” in either the PTs coded from the Investigator reported terms or the PTs coded from the ARAC diagnosis terms. The number (%) of patients with related events will be summarized by treatment group.

Allergic reactions

The number (%) of patients with events adjudicated as allergic reactions by ARAC and with events adjudicated by ARAC as possibly related to the IMP will be summarized by treatment group. All the allergic events reported by the Investigators 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 and causal relationship to the study drug (related, possibly related, unlikely related, not related), 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.

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.

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 clinical event. The number of events and rates in patient year will also be summarized as appropriate. In addition, a listing of patients with those events will be provided.

11.4.6.3 Analyses of laboratory variables

See [Section 9.2.2.3](#).

The number (%) of patients with PCSA at any evaluation during the on-treatment period will be summarized for each clinical laboratory test within each treatment group. The summaries will include patients in the safety population who have at least one laboratory test performed during the on-treatment period and, when required by the definition of the abnormality, with an available baseline value and available laboratory normal range.

Descriptive statistics will be used to summarize the laboratory test results and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Shift tables and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listing will be provided with flags indicating the out of laboratory range values as well as the PCSA values.

Drug-Induced Liver Injury

The liver function tests, namely AST, ALT, alkaline phosphatase 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 of 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/International normalized ratio (INR), creatine phosphokinase, serum creatinine, complete blood count, Immunoglobulin 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.

11.4.6.4 Analyses of vital sign variables

See [Section 9.2.2.4](#).

The number and percentage of patients with PCSA at any evaluation during the on-treatment period will be summarized for each vital sign parameter within each treatment group. The summaries will include patients in the safety population who have at least one parameter to be analyzed during the on-treatment period. When the PCSA definition involves the change from the baseline value, patients need also to have a baseline value to be included in the summaries.

Descriptive statistics will be used to summarize the results for systolic and diastolic blood pressure and heart rate, and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Tabular and graphical methods may be used to present the results for parameters of interest.

Listings will be provided with flags indicating the PCSA values.

11.4.6.5 Analysis of 12 lead ECG status

See [Section 9.2.2.5](#).

A shift table will be provided to present the ECG on-treatment status according to the baseline status within each treatment group.

11.4.6.6 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 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 antibodies, will be listed and summarized by visit using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum and maximum.

11.5 INTERIM ANALYSIS

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

The primary analysis of the efficacy and safety will be 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.

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).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Association Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Association Assemblies, and the International Council for Harmonization (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on afro American population for FDA) (29).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;

- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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