Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind Placebo-controlled and Open-label Active-controlled, Parallel-group, Multicenter, Dose-ranging Study to Evaluate the Safety and Efficacy of JNJ-64565111 in Non-diabetic Severely Obese Subjects

Protocol 64565111OBE2001; Phase 2b
AMENDMENT 1

JNJ-64565111 (efinopegdutide)

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This compound is being investigated in Phase 2 clinical studies.

This study will be conducted under United States Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	08 February 2018
Amendment 1	23 August 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (23 August 2018)

The overall reason for the amendment: The overall reasons for the amendment are to provide further instructions on the safety monitoring of subjects with adverse events of moderate and severe vomiting that may lead to dehydration, and to add a discontinuation criterion for subjects who experience severe vomiting.

Applicable Section(s)	Description of Change(s)
Rationale: To provide further instructions on the management of subjects with adverse events of moderate and severe vomiting that may lead to dehydration.	
9.10, Safety Evaluations	Added: • Instructions on the monitoring, evaluation, and follow-up of subjects with moderate and severe vomiting • Instruction on how to manage study drug in subjects with moderate or severe vomiting • Clarification on the use of anti-emetics to treat subjects with moderate and severe vomiting.
Rationale: To add a discontinuation criterion about vomiting.	
10.2, Discontinuation of Study Treatment/Discontinuation from the Study	Added discontinuation criterion "Subject experiences an episode of vomiting assessed as "severe" lasting more than 24 hours and considered to be at least possibly related to study drug without any other potential cause (eg, viral gastroenteritis, food-borne illness)."
Rationale: To fix minor errors.	
10.2, Discontinuation of Study Treatment/Discontinuation from the Study	Added discontinuation criterion that the investigator can formally unblind the subject's treatment allocation.

SYNOPSIS

A Randomized, Double-blind Placebo-controlled and Open-label Active-controlled, Parallel-group, Multicenter, Dose-ranging Study to Evaluate the Safety and Efficacy of JNJ-64565111 in Non-diabetic Severely Obese Subjects

JNJ-64565111 (efinopegdutide, formerly designated as HM12525A, developed by Hanmi Pharmaceuticals) is a synthetic, modified oxyntomodulin (OXM) peptide conjugated to a constant region of a human immunoglobulin G4 fragment to prolong the plasma half-life of the peptide.

Oxyntomodulin is an endogenous peptide secreted by cells in the gut in response to nutrient ingestion. Oxyntomodulin is a dual agonist, acting at both the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) and the glucagon receptor (GCGR). These combined actions at the GLP-1R (enhanced glucose-stimulated insulin secretion and suppression of food intake) and the GCGR (suppression of food intake, increased energy expenditure, and improved lipid metabolism) suggest that OXM-based therapeutics could provide several benefits to obese patients and might provide superior weight loss as compared to currently available weight-management medications.

In animal models of obesity, JNJ-64565111 improves lipid profiles and causes significant weight loss.

The goal of this dose-range-finding study is to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) over a range of JNJ-64565111 doses that yield therapeutic benefit in subjects with severe obesity (body mass index [BMI] ≥35 to ≤50 kg/m^2) to provide information for selecting JNJ-64565111 dose(s) to be assessed in Phase 3 studies.

OBJECTIVES AND HYPOTHESES

Objectives

Primary Objectives

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with placebo after 26 weeks of treatment on:

- the percentage change in body weight from baseline
- safety and tolerability

Secondary Objectives

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with placebo after 26 weeks of treatment on:

- the proportion of subjects with ≥5% weight loss from baseline
- the proportion of subjects with ≥10% weight loss from baseline
- the absolute change in body weight from baseline

Exploratory Objectives

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with placebo after 26 weeks of treatment on:

- the change in BMI from baseline
- the change in waist circumference from baseline

- the change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides) from baseline
- the change in fasting plasma glucose (FPG) from baseline
- the change in fasting insulin from baseline
- the change in fasting C-peptide from baseline
- the changes in Homeostasis Model Assessment for B cell function (HOMA-B) and HOMA-insulin resistance (IR) from baseline
- the change in systolic blood pressure (SBP) from baseline
- the change in diastolic blood pressure (DBP) from baseline
- the change in pulse rate from baseline
- the change in pulse-pressure product from baseline
- in a subset of subjects participating in the 24-hour ambulatory blood pressure monitoring (ABPM) assessment, the changes from baseline in 24-hour SBP, DBP, pulse rate, and pulse-pressure product
- Pharmacokinetic (PK) exposure
- the change from baseline in scores on the Impact of Weight on Quality of Life-Lite (IWQOL-Lite), single item Ease of Weight Management, and the Patient Activation Measure (PAM)
- in English-speaking subjects in selected countries only, the change from baseline in scores on the eating-related concept question (ERCQ) and the Patient-Reported Outcomes Measurement Information System (PROMIS) physical function short form 8b (PROMIS SF 8b) (Note: the Patient Global Impression Status [PGIS] and Patient Global Impression of Change [PGIC] will be used to calculate responder definitions for these new instruments only and are not exploratory objectives.)
- in English-speaking subjects in selected countries only, describe pre-trial goals and expectations as well as post-trial experiences qualitatively using the Anticipations of Clinical Trial Treatment (ACTT) pre-trial interviews and a modified Safety, Tolerability, and Efficacy Preview (STEP) exit interview

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with liraglutide after 26 weeks of treatment on:

- the absolute change and percentage change in body weight from baseline
- the proportion of subjects with ≥5% weight loss from baseline
- the proportion of subjects with ≥10% weight loss from baseline

Hypotheses

In non-diabetic severely obese subjects, treatment for 26 weeks with JNJ-64565111 compared with placebo leads to a greater:

Primary:

- percentage reduction in body weight

Secondary:

- proportion of subjects with ≥5% weight loss from baseline
- proportion of subjects with ≥10% weight loss from baseline

- absolute reduction in body weight from baseline

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled and open-label active-controlled, parallel-group, 5-arm, multicenter study. Non-diabetic, severely obese subjects who are ≥18 and ≤70 years of age and have a BMI ≥35 to ≤50 kg/m^2 will be assessed.

Subjects meeting all eligibility criteria will enter a 2-week run-in phase, which is to occur approximately 1 week after the screening visit and is designed to train the subject on subcutaneous (SC) self-injection and to establish the subject's ability to comply with the protocol-specified requirements. On Day 1, approximately 440 subjects who continue to meet eligibility criteria will be randomly assigned in a 1:1:2:2:2 ratio to blinded treatment with placebo, JNJ-64565111 (5.0, 7.4, or 10.0 mg) or open-label liraglutide 3.0 mg, stratified by ABPM sub-study participation (yes or no), and then will enter a 26-week treatment phase. To maintain blinding, subjects randomly assigned to placebo will be subsequently randomly assigned in a 1:2:2 ratio to a placebo that matches the volume of the 5.0, 7.4, and 10.0 mg JNJ-64565111 doses (ie, approximately 11, 22, and 22 subjects, respectively). Post-randomization visits will be conducted at Weeks 2, 5, 10, 15, 20, 26/end-of-treatment (EOT) visit and 4-week serious adverse event (SAE) follow-up visit. The subset of subjects in the ABPM sub-study will have 2 additional visits (ie, Pre-Day 1 and Pre-Week 26). A subset of subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample. In addition, subjects in the open-label liraglutide treatment group will also be contacted preferably by telephone at Weeks 1, 3, and 4 to remind about the dosing titration (ie, to increase their dose of liraglutide by an 0.6 mg dose increment weekly).

The efficacy evaluation will include the percentage change in body weight from baseline as the primary efficacy endpoint.

Safety evaluations will include the monitoring of adverse events (AEs) (including protocol-specified AEs of interest), vital sign measurements, clinical laboratory tests (including calcitonin, lipase, amylase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, sodium), urinalysis, review of concomitant medications, and serum pregnancy testing.

Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) and the 4-week SAE follow-up. Subjects that discontinue study drug early will continue in the study and be assessed with the off-treatment procedures at the subsequent visit(s) per the Time and Events visit schedule, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 26 visit. These off-treatment visits will include assessment and collection of SAEs, specific AEs of interest (ie, major adverse cardiovascular event [MACE] events, acute pancreatitis, and possible cases of thyroid neoplasm), vital signs (including body weight), and concomitant medications. Subjects who discontinued prior to Week 26 and have the 4-week SAE follow-up visit do not need to return for a second 4-week SAE follow-up visit. All subjects, except those who died, were lost to follow-up, or have a withdrawn consent, will have a follow-up visit approximately 5 weeks after the last dose of study drug for JNJ-64565111-treated or placebo-treated subjects and 4 weeks after the last dose of study drug for liraglutide-treated subjects to collect any SAEs. For subjects randomly assigned to JNJ-64565111 or placebo, blood samples for immunogenicity anti-drug antibody and PK assessments will also be obtained at the SAE follow-up visit.

A non-trough PK visit will occur at selected sites and will involve approximately 180 subjects (approximately 45 subjects each in the placebo, JNJ-64565111 5 mg, JNJ-64565111 7.4 mg, and JNJ-64565111 10 mg groups). A 24-hour ABPM assessment will be performed at selected sites and will involve approximately 120 subjects (approximately 15 subjects each in the placebo and JNJ-64565111 5 mg groups, and 30 subjects each in the JNJ-64565111 7.4 mg, JNJ-64565111 10 mg, and liraglutide groups). During the run-in phase, these subjects will wear the ABPM device for at least 24 hours 1 or

2 days prior to the Day1/Randomization visit. The ABPM readings will be masked. When subjects return for the Day 1 visit, ABPM readings will be assessed for subject eligibility into the ABPM sub-study based on the ABPM requirements. After randomization, subjects participating in the ABPM sub-study will be required to repeat a 24-hour ABPM assessment 1 or 2 days prior to the Week 26/ EOT in subjects who have not withdrawn consent, died or were lost to follow-up. For subjects treated with JNJ-64565111 or matching placebo, every effort should be made to have the procedure performed within 7 days from the previous dose of study drug.

The IWQOL-Lite, Ease of Weight Management, and PAM will be administered at all sites to all subjects. The PROMIS SF 8b and ERCQ along with both the PGIS and PGIC will be administered at selected sites and will involve approximately 120 English-speaking subjects. These instruments are intended to measure eating-related concepts such as hunger, appetite, cravings, and satiety, and physical function.

Subjects who withdraw from the study will not be replaced.

The overall study duration is approximately 33 weeks and comprises of 3 phases:

Pre-treatment phase

- Screening phase: 1 week
- Run-in (injection-training) phase: 2 weeks

Treatment phase (double-blind and open-label arms)

- Placebo- and active-controlled treatment phase: 26 weeks

Post-treatment phase (SAE follow-up visit): 4 weeks

Approximately 440 subjects will be randomly assigned in a 1:1:2:2:2 ratio to one of the following once SC treatments:

- 55 subjects to double-blind placebo matching JNJ-64565111,
- 55 subjects to double-blind JNJ-64565111 5.0 mg,
- 110 subjects to double-blind JNJ-64565111 7.4 mg,
- 110 subjects to double-blind JNJ-64565111 10.0 mg, and
- 110 subjects to open-label liraglutide 3.0 mg.

SUBJECT POPULATION

Non-diabetic, severely obese subjects who are ≥18 and ≤70 years of age and have a BMI ≥35 to ≤50 kg/m^2 will be assessed.

DOSAGE AND ADMINISTRATION

Pre-Randomization Open-label Placebo

At the Week -2 visit, subjects will be instructed on the use of pre-filled safety injectors to perform SC self-injections, and will be asked to perform a self-injection in the presence of the study-site staff. Only subjects who express willingness and demonstrate the ability to administer daily SC injections are eligible to participate in the study. To assess compliance with the dosing regimen, eligible subjects will be dispensed pre-filled safety injectors containing 0.5 mL open-label placebo and instructed to perform ***once-weekly*** self-injections at home during the 2-week run-in phase, as well as keep a study drug diary of their injection schedule.

Post-randomization Double-blind JNJ-64565111 or Matching Placebo and Open-label Liraglutide

Double-blind JNJ-64565111 or Matching Placebo

Double-blind JNJ-64565111 or matching placebo supplies should be stored in the refrigerator at 36 to 46°F (2 to 8°C) and kept in their carton until ready for use and protected from direct heat and light. Blinded study drug can be left out at room temperature up to 8 hours. Avoid shaking blinded study drug.

JNJ-64565111 will be supplied as a solution for injection at a concentration of 20.0 mg/mL. Blinded study drug will be provided in pre-filled safety injectors with attached SC needle, pre-filled with nominal volumes of 0.25, 0.37, or 0.50 mL of JNJ-64565111 (5.0, 7.4, or 10.0 mg, respectively) or 1 of 3 matching volumes of placebo.

On Day 1, subjects randomly assigned to the double-blind treatment arms will receive a supply of their study drug (or matching placebo), and will be reminded of the once-weekly dosing regimen and to record the date and time of each administered dose in the study drug diary. Subjects will self-administer the first dose of JNJ-64565111 or matching placebo at the site under the supervision of study staff.

Subjects will be reminded that if the day of their once-weekly injection coincides with the day of a clinic visit, subjects are not to inject JNJ-64565111 or matching placebo before arriving at the clinic; once all study visit procedures have been completed, subjects may self-administer blinded study drug (or matching placebo) either at the study site or once they have returned home that day.

JNJ-64565111 or matching placebo will not be titrated. Subjects will remain on their assigned dosages throughout the treatment phase (ie, until Week 26 or early discontinuation of study drug).

Open-label Liraglutide (Saxenda®)

Commercially available supplies of liraglutide will be dispensed to subjects randomly assigned to the open-label liraglutide arm of the study. Liraglutide is supplied as a pre-filled, multi-dose pen that delivers once-daily doses of 0.6, 1.2, 1.8, 2.4, or 3.0 mg (6.0 mg/mL, 3.0 mL).

On Day 1, subjects randomly assigned to open-label liraglutide will receive instruction on the use of the pre-filled multi-dose pen. Subjects will self-administer the first dose of study drug at the site under the supervision of study staff.

The dosage of liraglutide to be used in this study is consistent with the approved labeling for its use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients. The starting dosage of liraglutide on Day 1 will be 0.6 mg/day. At the beginning of Weeks 1, 2, 3, and 4, subjects will be contacted preferably by telephone and instructed to up-titrate their daily dose to 1.2, 1.8, 2.4, and 3.0 mg in 0.6 mg weekly increment. At Week 5, subjects will return to the clinic and should already be up-titrated to their daily dose of 3.0 mg. Subjects should remain on this dose for the remainder of the treatment phase.

For subjects who experience significant gastrointestinal intolerance within the weeks prior to the Week 5 visit, up-titration of liraglutide may be delayed by 1 week. The reason for delaying up-titration will be documented on the study drug diary and electronic case report form (eCRF). If a subject cannot tolerate the 3.0 mg dose of liraglutide by Week 6, they should be discontinued from study treatment, as the efficacy of liraglutide for weight management has not been established at lower doses.

Drug Administration

Injections of JNJ-64565111 (or matching placebo) and liraglutide can be done at any time of day irrespective of meals. However, it is preferable that the general time of day (ie, morning, evening, just prior to bed, etc.) for injecting study drug be kept consistent, to the extent possible.

Double-blind JNJ-64565111 or Matching Placebo

Subjects randomly assigned to double-blind JNJ-64565111 (or matching placebo) will be instructed to administer study drug SC once-weekly for the entire duration of the 26-week treatment phase or until early discontinuation. Subjects will be instructed to inject to the 4 quadrants of the anterior abdominal wall. For consistency, and to avoid dosing in the same abdominal area, subjects should be instructed to begin in one quadrant and on subsequent dosing weeks proceed in the next quadrant in a counterclockwise manner.

JNJ-64565111 (or matching placebo) should be taken on the same day of the week throughout the study (ie, the regularly scheduled study drug day). If the day of the once-weekly injection coincides with the day of a clinic visit, subjects are NOT to inject JNJ-64565111 (or matching placebo) before arriving at the clinic. Instead, AFTER all study visit procedures have been completed, subjects may self-administer blinded study drug either at the study site or once they have returned home.

Subjects are to record the date and time of study drug administration on the study drug diary. Subjects should mark a calendar to remind them of when to take the next weekly dose.

Subjects in the JNJ-64565111 (or matching placebo) groups should be instructed not to take 2 doses within 3 days (72 hours) of each other. If a subject misses taking the next dose of JNJ-64565111 (or matching placebo) on their regularly scheduled study drug day, the missed dose should be taken as soon as possible, if there are at least 3 days (72 hours) until their next regularly scheduled study drug day. If there are less than 3 days remaining, the subject should skip the missed dose and take the next dose on their regularly scheduled study drug day.

Open-label Liraglutide (Saxenda®)

Subjects randomly assigned to open-label liraglutide will be instructed to administer study drug SC once daily for the entire duration of the 26-week treatment phase or until early drug discontinuation.

Liraglutide solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

Subjects may administer liraglutide SC either in the abdomen, thigh, or upper arm. The injection site may be changed at any time. If the same injection area is being used, subjects will be instructed to choose different injection sites in that area (eg, rotating through different abdominal quadrants).

On the days of scheduled clinic visits, subjects in the open-label liraglutide group should be instructed NOT to inject liraglutide before arriving at the clinic. Instead, AFTER all study visit procedures have been completed, subjects may self-administer liraglutide either at the study site or once they have returned home.

If a dose of liraglutide is missed, the once-daily regimen should be resumed with the next scheduled dose. An extra dose should not be taken to make up for the missed dose.

- After an interruption of more than 6 days, the subject who had already reached the 3.0 mg dose level should re-initiate liraglutide with a starting dose of 1.8 mg and re-up-titrate to 3.0 mg.
- For an interruption of 4 to 6 days in duration, it will be up to investigator's judgment to assess whether the subject should re-start at 3.0 mg daily dose, or re-start at 1.8 mg or 2.4 mg.

If, after an interruption of at least 4 days, the subject re-starts at a dose of 1.8 mg or 2.4 mg, the dose should be up-titrated in 0.6 mg increment every 7 days until the full dosage of 3.0 mg is reached.

Drug Storage

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Double-blind JNJ-64565111 or Matching Placebo

Double-blind JNJ-64565111 or matching placebo supplies should be stored in the refrigerator at 36 to 46°F (2 to 8°C) and kept in their carton until ready for use and protected from direct heat and light. Blinded study drug or matching placebo can be left out at room temperature up to 8 hours. Avoid shaking blinded study drug.

Open-label Liraglutide (Saxenda®)

Prior to first use, liraglutide pens should be stored in the refrigerator at 36 to 46°F (2 to 8°C) and protected from direct heat and light. Do not store in the freezer or directly adjacent to the refrigerator cooling element. Liraglutide pens should not be frozen; if the pen is frozen, it should be thrown away.

After initial use of the liraglutide pen, it is preferably to be stored in a refrigerator (36 to 46°F; 2 to 8°C). Alternatively, it may be stored at controlled room temperature (59 to 86°F; 15 to 30°C) for up to 30 days only. The pen cap should be kept on when not in use.

To reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy, subjects should be instructed to always remove and safely discard the needle after each injection and store the liraglutide pen without an injection needle attached.

EFFICACY EVALUATIONS

Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage change in body weight from baseline to Week 26 between JNJ-64565111 compared to placebo.

Secondary and Exploratory Efficacy Endpoints

The secondary measures of efficacy at Week 26 include proportion of subjects with ≥5% and ≥10% weight loss from baseline, and absolute change in body weight from baseline. Exploratory efficacy endpoints at Week 26 include change from baseline in BMI, waist circumference, fasting lipids (total cholesterol, LDL-C, HDL-C, and triglycerides), FPG, fasting insulin, fasting C-peptide, SBP, DBP, pulse rate, pulse-pressure product, PK exposure, and patient-reported outcomes (PROs) (ie, changes in IWQOL-Lite, single item Ease of Weight Management, and PAM).

Additional exploratory endpoints assessed in English-speaking subjects in selected countries only at Week 26 include PROs (ie, changes in ERCQ and PROMIS SF 8b), changes in qualitative assessments of pre-trial expectations and post-trial experiences using the ACTT pre-trial interviews, and a modified STEP exit interview.

The effects of JNJ-64565111 compared with liraglutide on the percentage change and absolute change in body weight from baseline and the proportion of subjects with ≥5% and ≥10% weight loss from baseline will also be assessed at Week 26.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

In subjects randomly assigned to JNJ-64565111 or matching placebo (but not in subjects randomly assigned to open-label liraglutide), venous blood samples will be collected according to the Time and Events Schedule for determination of serum trough concentrations of JNJ-64565111 and attainment of steady-state concentrations, as well as for detection and characterization of anti-JNJ-64565111 antibodies.

On the days of the clinic visits at which PK samples are to be obtained, subjects are not to inject the study drug before arriving at the clinic. The exact dates and times of the study drug previous injection and blood sampling must be recorded in the eCRF or laboratory requisition form.

In a subset of subjects, non-trough PK samples will be collected 4 days (±1 day) after the first dose of JNJ-64565111 or matching placebo.

SAFETY EVALUATIONS

Safety evaluations will include the monitoring of AEs (including protocol-specified AEs of interest), vital sign measurements, clinical laboratory tests (including serum chemistry, CBC, calcitonin, lipase, and amylase), and serum pregnancy testing. Adverse events of interest include MACE (ie, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), hypotension-related AEs, acute pancreatic events (ie, AEs of pancreatitis, AEs of serious or severe abdominal pain leading to suspicion of pancreatitis, and confirmed lipase or amylase elevations ≥3× upper limit of normal), calcitonin elevation, and thyroid neoplasm.

STATISTICAL METHODS

Analysis Sets

The intent-to-treat (ITT) analysis set will include all subjects who are randomly assigned to a treatment group and have a baseline measurement of body weight. The modified intent-to-treat (mITT) population includes all ITT subjects who had at least 1 post-baseline measurement of body weight within 7 days following a dose of study drug. The completers' analysis set will consist of all mITT subjects who have completed 26 weeks of double-blind treatment (ie, documented in the eCRF by the investigators that the subject has completed participation in the study through the Week 26 visit). The safety analysis set will include all randomized subjects who have received at least one dose of study drug.

The primary efficacy analysis, to demonstrate the superiority of JNJ-64565111 compared to placebo on percentage reduction in body weight from baseline to Week 26, as well as all secondary efficacy analyses, will be based on the mITT analysis set and will include only those measurements taken up to and including the last dose of study drug plus 7 days. A secondary analysis of the primary and secondary efficacy endpoints will be based on the ITT population. This analysis will include all measurements. Sensitivity analyses based on the completers' analysis set will also be performed for the primary endpoint.

Efficacy data will be analyzed according to the initial randomization assignment, regardless of the actual treatment received. Safety data will be analyzed according to the predominant treatment received, in the event that a subject receives a treatment other than that to which he/she is randomly assigned.

Sample Size Determination

A total of approximately 440 subjects will be randomized into this study with approximately 55 subjects per group allocated to placebo and JNJ-64565111 5.0 mg group, and approximately 110 subjects per group allocated to each of the other 3 groups: JNJ-64565111 7.4 mg, JNJ-64565111 10.0 mg, and open-label liraglutide 3.0 mg. Sample size was determined based on assessing the primary hypothesis that the treatment with JNJ-64565111 for 26 weeks leads to greater percentage reduction in body weight compared with placebo as well as the exploratory hypothesis that the treatment with JNJ-64565111 leads to greater percentage reduction in body weight compared with open-label liraglutide.

Assuming a common standard deviation of 7% with respect to percent change in body weight at Week 26 and a 2-sided Type 1 error rate of 0.05, it is estimated that a sample size of 55 randomized subjects per group will have approximately 90% power to detect a treatment difference of 4.4%, 110 randomized subjects per group will have approximately 90% power to detect a treatment differences of 3.1%.

Safety Analyses

The evaluation of safety will be based on the incidence of AEs and changes in clinical laboratory test results and vital sign results (SBP, DBP, and pulse rate). Summaries of AEs, clinical laboratory test results, and vital sign results will be provided by treatment group.

Efficacy Analyses

All hypotheses will be tested 2-sided at a 5% significance level unless otherwise specified.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage change in body weight between JNJ-64565111 and placebo from baseline to Week 26.

The primary efficacy endpoint will be analyzed based on the mITT analysis set using a mixed model for repeated measures (MMRM). The analysis will use the observed data through Week 26 while on treatment (up to the last dose of study drug plus 7 days) and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the fixed, continuous, covariates of baseline body weight and baseline-by-visit interaction. An unstructured covariance will be used to model the within-patient errors. The treatment comparisons will be made between each of the JNJ-64565111 treatment groups and placebo at Week 26 based on this model.

A secondary analysis of the primary endpoint will be based on the ITT population and will employ pattern mixture models using multiple imputation methods. Responses for subjects who discontinued from the study earlier than Week 26 will be imputed based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. The imputation will be done within groups defined by randomized treatment. Data will be analyzed using the same model as in the primary analysis. The treatment comparisons between each of the JNJ-64565111 treatment groups and placebo will be made at Week 26. Details of this approach will be provided in the Statistical Analysis Plan (SAP).

Finally, the primary efficacy endpoint will be analyzed based on the completers' analysis set. Additional analysis using a MCP-Mod (Multiple Comparison Procedure – Modeling) approach will be performed to explore the dose-response relationship.

Secondary Efficacy Endpoints

Secondary efficacy analyses at Week 26 will include proportion of subjects with ≥5% and ≥10% weight loss and the absolute change in body weight from baseline.

The continuous secondary endpoints (ie, absolute change in body weight from baseline) at Week 26 will be analyzed with an MMRM model similar to the primary efficacy endpoint in the mITT analysis set.

The categorical secondary efficacy endpoint (ie, the proportion of subjects with ≥5% weight loss and the proportion of subjects with ≥10% weight loss at Week 26) will be analyzed longitudinally using a generalized linear mixed model. The model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline body weight, and baseline-by-visit interactions. An unstructured covariance will be used to model the within-patient errors. The odds ratio and associated p-value for the treatment comparison between each of the JNJ-64565111 treatment groups versus placebo at Week 26 based on this model will be provided.

A secondary analysis of the secondary endpoints will be based on the ITT population and will employ pattern mixture models using multiple imputation methods based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. For the categorical endpoints, response status will be determined from the imputed continuous response based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements.

Multiplicity Adjustment

The type I error will be strongly controlled at α=5% for each of primary endpoint and secondary endpoints. The Dunnett's method will be used to adjust the multiplicity of the comparisons of each of the JNJ-64565111 doses versus placebo for the primary efficacy endpoint of the percentage change in body weight and the secondary endpoint of the absolute change in body weight. The Bonferroni correction will be used to adjust the multiplicity of the comparisons for the secondary endpoints of the proportion of subjects with weight loss ≥5% and ≥10%.

Exploratory Endpoints

The exploratory analysis of the assessments between the JNJ-64565111 treatment groups and placebo include the following to Week 26:

- the change in BMI from baseline
- the change in waist circumference from baseline
- the change in fasting lipids (total cholesterol, LDL-C, HDL-C, and triglycerides) from baseline
- the change in FPG from baseline
- the change in fasting insulin from baseline
- the change in fasting C-peptide from baseline
- the changes in HOMA-B and HOMA-IR from baseline
- the change in SBP from baseline
- the change in DBP from baseline
- the change in pulse rate from baseline
- the change in pulse-pressure product from baseline
- in a subset of subjects participating in the 24-hour ABPM assessment, the changes in 24-hour SBP, DBP, pulse rate, and pulse-pressure product

Change from baseline in total cholesterol, LDL-C, HDL-C, and triglycerides, change from baseline in fasting insulin, change from baseline in SBP, change from baseline in DBP, and change from baseline in pulse-pressure rate will be analyzed using a MMRM model similar to that used to analyze the primary efficacy endpoint.

The exploratory PRO endpoints will be summarized descriptively at baseline and over time. These endpoints include:

- IWQOL-Lite total and physical function, self-esteem, sexual life, public distress, and work domain scores
- Ease of Weight Management total scores
- PAM total scores
- ERCQ domain scores and PROMIS SF 8b total scores (in English-speaking subjects in selected countries only)
- Describe pre-trial goals and expectations as well as post-trial experiences qualitatively using the ACTT Pre-trial interviews and a modified STEP exit interview (in English-speaking subjects in selected countries only)

The exploratory analysis of the assessments between the JNJ-64565111 treatment groups (7.4 mg and 10 mg) and liraglutide on the percentage change in body weight will also be performed. The same analysis model used for the comparisons with placebo on the primary efficacy endpoint will be used for these assessments.

The exploratory analysis of the assessments between the JNJ-64565111 treatment groups (7.4 mg and 10 mg) and liraglutide on ≥5% weight-loss responders and ≥10% weight-loss responders and the absolute change in body weight at Week 26 will also be performed. The same analysis models used for the comparisons with placebo will be used for these assessments.

Interim Analysis

An interim analysis will be performed when approximately 90% of subjects have either completed or discontinued prior to approximately 10 weeks of study drug treatment. The objective of this interim analysis is to identify active treatment groups, if any, associated with safety or tolerability issues and to facilitate planning of the Phase 3 program. The dissemination of the interim analysis results will be limited to an internal data monitoring committee (DMC), and will not be shared with investigators, subjects, or the sponsor staff who will continue to be involved in the conduct of the study before the final database lock. The operational details of the interim analysis will be provided in the DMC SAP.

TIME AND EVENTS SCHEDULE

Protocol Activity	Pre-treatment			Treatment												Post-treatment
	Screening	Run-In														
	Wk -3	Wk -2	Pre-Day 1 (ABPM Only)[a]	Day 1 (Random-ization)	Day 4	Wk 1 (RC)	Wk 2	Wk 3 (RC)	Wk 4 (RC)	Wk 5[b]	Wk 10[b]	Wk 15[b]	Wk 20[b]	Pre-Wk 26 (ABPM Only)[a]	Wk 26/ EOT[c]	4-Week SAE F/U[d]
Screening/Administrative																
Informed consent [e]	X															
Inclusion/exclusion criteria	X	X		X												
Medical history & demographics	X															
Prior therapy reporting and review [f]	X	X		X												
IWRS log-in/tracking	X	X		X						X	X	X	X		X	
Randomization				X												
Study Drug Administration																
Show and/or describe injection device of JNJ-64565111/matching placebo	X	X														
Show and/or describe injection device of liraglutide	X			X												
Dispense open-label placebo		X														
Dispense open-label liraglutide or double-blind JNJ-64565111/ matching placebo				X						X	X	X	X			
Drug titration (liraglutide arm only)[g]						X	X	X	X							
Injection at study site[h]		X		X												
Dispense study drug diary		X		X						X	X	X	X			
Review study drug diary				X						X	X	X	X		X	
Run-in compliance assessment				X												
Drug accountability				X						X	X	X	X		X	

Protocol Activity	Pre-treatment			Treatment												Post-treatment
	Screening	Run-In														
	Wk -3	Wk -2	Pre-Day 1 (ABPM Only)[a]	Day 1 (Random-ization)	Day 4	Wk 1 (RC)	Wk 2	Wk 3 (RC)	Wk 4 (RC)	Wk 5[b]	Wk 10[b]	Wk 15[b]	Wk 20[b]	Pre-Wk 26 (ABPM Only)[a]	Wk 26/ EOT[c]	4-Week SAE F/U[d]
Survey on self-administration of study drug[i]										X						
Clinical Procedures																
Physical examination	X														X	
Vital signs (pulse rate and BP, in triplicate)[j]	X			X						X	X	X	X		X	
Weight[j]	X			X						X	X	X	X		X	
Height[j]	X															
Waist circumference [k]				X								X			X	
12-lead ECG (local)		X														
24-hour ABPM sub-study [a]																
Set up ABPM device and dispense ABPM diary			X											X		
Return ABPM device, transfer ABPM data, generate and review ABPM report				X											X	
Review ABPM diary				X											X	
Laboratory Assessments [l]																
Fasting lipid profile [m]	X			X								X			X	
Serum chemistry	X			X			X			X	X	X	X		X	
FPG	X			X						X	X	X	X		X	X[n]
HbA_{1c}	X											X			X	
Fasting insulin				X											X	
Fasting C-peptide				X											X	
Hematology				X								X			X	
Calcitonin	X			X								X			X	
Serum ß-hydroxybutyrate				X						X	X	X	X		X	
Urine dipstick/ urinalysis				X											X	
Serum pregnancy test [o]	X														X	

Protocol Activity	Pre-treatment			Treatment												Post-treatment
	Screening	Run-In														
	Wk -3	Wk -2	Pre-Day 1 (ABPM Only)[a]	Day 1 (Random-ization)	Day 4	Wk 1 (RC)	Wk 2	Wk 3 (RC)	Wk 4 (RC)	Wk 5[b]	Wk 10[b]	Wk 15[b]	Wk 20[b]	Pre-Wk 26 (ABPM Only)[a]	Wk 26/ EOT[c]	4-Week SAE F/U[d]
Follicle-stimulating hormone [p]	X															
Trough pharmacokinetic and Immunogenicity ADA samples (For subjects in JNJ-64565111 or matching placebo groups only) [q]				X			X			X	X	X			X	X
Non-trough pharmacokinetic sample (For subjects in JNJ-64565111 or matching placebo groups only) [r]					X											
Fasting plasma, serum, and urine archive samples for exploratory research [m]				X											X	
Interviews																
ACTT interview (subset of subjects)[s]				X												
STEP interview (subset of subjects)[s]															X	
Subject Counseling and Ongoing Review/Assessments																
Assessment of subjects' status and reinforcement of study procedures							X									
Diet and exercise counseling [t]				X						X	X	X	X			
Adverse Event reporting and review		X		X			X			X	X	X	X		X	X
Record concomitant therapy[f]				X						X	X	X	X		X	

ABPM = Ambulatory blood pressure monitoring; ACCT = Anticipations of Clinical Trial Treatment; ADA = anti-drug antibodies; BP = blood pressure; ECG = Electrocardiogram; EOT = End-of-treatment; FPG = fasting plasma glucose; FSH = Follicle-stimulating hormone; F/U = follow-up; HbA_{1c} = Hemoglobin A_{1c}; IWRS = interactive web response system; PK = Pharmacokinetics; RC = remote contact (preferably by telephone); SAE = serious adverse event; STEP = Safety, Tolerability, and Efficacy Preview; Wk = week.

a) A 24-hour ABPM will be obtained in a subset of subjects at selected sites. At the Week -2 visit, subjects participating in the ABPM sub-study will be asked to return to the study site 1 or 2 days prior to the Day 1 and Week 26/ EOT visits to be fitted with an ABPM device. Subjects will return the device at the Day 1 and Week 26/EOT visits. Instructions for collecting ABPM measurements can be found in the procedural manual.
b) At some time between Weeks 2, 5, 10, 15, 20, and 26 visits, study-site staff is encouraged to contact subjects preferably by telephone to reinforce the adherence to diet and exercise, study drug dosing reminder, assessment of subjects' status, and compliance with the protocol procedures (eg, diary completion reminder).
c) Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation). Subjects that discontinue study drug early will continue in the study and be assessed with the off-treatment procedures at the subsequent visit(s) per the Time and Events visit schedule, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 26 visit. These off-treatment procedures will include assessment and collection of SAEs, specific AEs of interest (ie, MACE events, acute pancreatitis, and possible cases of thyroid neoplasm), vital signs (including body weight) and concomitant medications.
d) The SAE follow-up visit will be conducted for all subjects approximately 5 weeks after the last dose of study drug for JNJ64565111/placebo-treated subjects and 4 weeks after the last dose of study drug for liraglutide-treated subjects to collect SAEs unless the subject has died, has been lost to follow-up, or has withdrawn consent. For subjects randomly assigned to double-blind JNJ-64565111 or placebo, blood samples will also be collected for PK and immunogenicity anti-drug antibody (ADA) measurement. Subjects who prematurely discontinue study drug for any reason prior to Week 26 and have not withdrawn consent, will continue (off-treatment) in the study following the EOT visit and undergo the off-treatment procedures based on the predefined study visit schedule.
e) Informed Consent must be signed at the screening visit before any study procedures are performed.
f) Record any medications taken from up to 30 days before screening until the first dose of double-blind study drug on Day 1 (baseline) as pre-study therapy in the corresponding eCRF. Concomitant therapy includes all medications since the first dose of study drug on Day 1.
g) The starting dosage of liraglutide on Day 1 will be 0.6 mg once daily. Subjects will be contacted preferably by telephone weekly during the first 4 weeks of the study and instructed to increase their dose of liraglutide by an 0.6 mg dose increment every 7 days, until they have reached the full dosage of 3.0 mg once daily by Week 5. Subjects will then continue on the 3.0 mg once-daily dosage for the remainder of the study. For subjects who experience significant gastrointestinal intolerance prior to the Week 5 visit, up-titration of liraglutide may be delayed by 1 week. If a subject cannot tolerate the 3.0 mg dose of liraglutide by Week 6 they should be discontinued from study treatment.
h) Subjects will be asked to perform a self-injection of open-label JNJ-64565111-matching placebo (Week -2) or their randomly assigned study drug (Day 1) at the study site in the presence of the study-site staff. After Day 1, injections may be performed by the subject at home.
i) A survey will be given to English-speaking subjects in selected countries to assess subject satisfaction with the experience of self-administering JNJ-64565111 or matching placebo or liraglutide. The PI should use their discretion to determine whether the subject is sufficiently fluent in English to take the survey.
j) Blood pressure and pulse rate: 3 seated readings will be recorded in the source and eCRF. See Attachment 2, Method of Blood Pressure and Pulse Rate Measurement.
k) Body weight will be measured using a calibrated scale; subjects should be weighed wearing underwear and a gown. Note: if disrobing for weighing is logistically impossible, the subject must be dressed as lightly as possible, with consistency from visit to visit; subjects will be instructed to take off their shoes and to empty their bladders before being weighed. Anthropometric measurements, for height, body weight and waist circumference measurement procedures, are described in Attachment 3.
l) Specific details about specimen collection, storage, packaging, and shipping will be provided in an operations manual from the central laboratory.
m) Subjects must fast for at least 8 hours before blood sample collection. If not fasting at the time of the screening visit, the subject should return to the site soon after the screening visit (and before the start of the run-in phase) to have a fasting sample collected.
n) FPG will be assessed in subjects who initiated metformin during the 26-week treatment period.
o) Serum (β-human chorionic gonadotropin [β-hCG]) pregnancy testing will be performed for all women of childbearing potential (ie, unless they are permanently sterilized or unless there is a documented history of their postmenopausal status, as defined in Section 4.1, Inclusion Criteria) at the screening and Week 26/EOT visits. Additional serum or urine pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study.
p) FSH will be measured in women >45 years of age with amenorrhea for at least 6 months and <18 months prior to screening.

q) For PK sampling, subjects will be instructed to refrain from taking the study drug in the morning before the clinic visit. The subject must report the time that the study drug was taken on the day preceding the clinic visit.
r) A subset of subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample.
s) Study entry (ACTT) and exit (STEP) interviews will be given to a subset of English-speaking subjects in selected countries. The PI should use their discretion to determine whether the subject is sufficiently fluent in English to take these surveys.
t) Counseling should be done by dietitians/nutritionists on Day 1/Day of Randomization to provide assessment and recommendation on a reduced-calorie diet and exercise regimen (see Attachment 4). At subsequent visits (Week 5, Week 10, Week 15 and Week 20), counseling and reinforcement of the recommended diet and exercise regimen will be conducted by a trained counselor.

TIME AND EVENTS SCHEDULE – PATIENT-REPORTED OUTCOMES

Protocol Activity	Pre-treatment				Treatment					
	Screening	Run-In								
	Week -3	Week -2	Week -1	Day 1 (Random-ization)	Week 15	Week 16	Week 20	Week 24	Week 25	Week 26/ EOT[a]
Patient-Reported Outcomes [b]										
IWQOL-Lite		X			X					X
Single item Ease of Weight Management		X			X					X
Patient Activation Measure (PAM)		X			X					X
Dispense diary containing Eating-related Concepts Questionnaire (ERCQ) (subset of subjects)		X			X		X			
Remote Site Contact to remind Completion of ERCQ diary (subset of subjects)								X		
Completion of ERCQ (subset of subjects)			X----------X[c]		X----------X[c]				X----------X[c]	
PROMIS Physical function short form (PROMIS SF 8b) (subset of subjects)		X		X	X					X
Patient Global Impression Status (PGIS) (subset of subjects)		X[d]			X[d]					X[d]
Patient Global Impression of Change (PGIC) (subset of subjects)					X[d]					X[d]

EOT = End-of-treatment; ERCQ = Eating-related Concepts Questionnaire; IWQOL-Lite = Impact Of Weight On Quality Of Life-Lite; PAM = Patient Activation Measure; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression Status; PROMIS = Patient-reported Outcomes Measurement Information System; PROMIS SF 8b = PROMIS Short Form 8b.

a) Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation). Subjects that discontinue study drug early will continue in the study and be assessed with the off-treatment procedures at the subsequent visit(s) per the Time and Events visit schedule, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 26 visit. These off-treatment procedures will include assessment and collection of SAEs, specific AEs of interest (ie, MACE events, acute pancreatitis, and possible cases of thyroid neoplasm), vital signs (including body weight) and concomitant medications.

b) All patient-reported outcome (PRO) assessments should be completed at the beginning of the clinic visit (whenever possible) for site visit-based assessments and completed at the same time each day in the same setting each day for home-based assessments as specified in the Time and Events Schedule, or at the time the subject discontinues the study drug or withdraws from the study, before all other evaluations, as specified in the Time and Events Schedule. Assessments (whenever possible) should be completed before any tests, procedures, or discussion of AEs or the subject's medical condition.
c) ERCQ diary should be completed at home for 7 consecutive days at these time points: (1) starting Week -1 to day before Day 1 for 7 consecutive days, (2) the next 1 or 2 days after Week 15 for 7 consecutive days, and (3) starting Week 25 up to the day before Week 26. For subjects who discontinue early from study drug, no ERCQ diary completion is required at the EOT visit.
d) PGIS and PGIC are needed to calculate responder definitions for new PRO instruments ERCQ and PROMIS SF 8b. These are not exploratory efficacy endpoints.

ABBREVIATIONS

5-HT_{2C}	5-hydroxytryptamine type 2C receptor
β-hCG	serum β-human chorionic gonadotropin
ABPM	ambulatory blood pressure monitoring
ACTT	anticipations of Clinical Trial Treatment
ADA	anti-drug antibodies
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{168hr}	area under the curve in the interval 0–168 hours
$AUC_{(0\text{-inf})}$	area under the curve from time zero (pre-dose) to extrapolated infinite time
$AUC_{(0\text{-last})}$	area under the curve from time zero (pre-dose) to last measurable concentration
$AUC_{(Tau)}$	area under the curve from time zero (pre-dose) to the end of dosing period
BMI	body mass index
bpm	beats per minute
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum observed plasma concentration
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CPK	creatinine phosphokinase
CT	computed tomography
CV	cardiovascular
DBP	diastolic blood pressure
DIO	diet-induced obese
DKA	diabetic ketoacidosis
DMC	data monitoring committee
DPP-IV	dipeptidyl peptidase-IV
ECG	electrocardiogram
eCRF(s)	electronic case report form(s)
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end-of-treatment
ERCQ	Eating-related Concept Questionnaire
EU	European Union
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GCGR	glucagon receptor
GCP	Good Clinical Practice
geo CV%	geometric coefficient variation
GI	gastrointestinal
GLP	Good Laboratory Practices
GLP-1	glucagon-like peptide-1
GLP-1R	GLP-1 receptor
HAART	highly Active Anti-retroviral therapy
HbA_{1c}	Hemoglobin A_{1c}
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
hERG	human ether-a-go-go-related gene
HMC001	human immunoglobulin G4 fragment
HMOXM25	GLP 1/Glucagon dual receptor agonist
HOMA-B	Homeostasis Model Assessment for B cell function

HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LS	Least-square
MACE	major adverse cardiovascular events
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	multiple endocrine neoplasia syndrome type 2
MI	myocardial infarction
mITT	modified intent-to-treat
mmHg	millimeters mercury
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OXM	oxyntomodulin
PAM	Patient Activation Measure
PD	pharmacodynamics
PEG	polyethylene glycol
PG	plasma glucose
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression Status
PI	Principal Investigator
PK	pharmacokinetics
PPG	postprandial plasma glucose
PPI	proton pump inhibitor
PQC	product quality complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS SF 8b	PROMIS physical function Short Form 8b
QTcR	Rautaharju corrected QT interval
REML	restricted maximum likelihood
SAD	single ascending dose
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous, subcutaneously
SD	standard deviation
SGLT2	sodium-glucose cotransporter 2
STEP	Safety, Tolerability, and Efficacy Preview
SUSAR(s)	suspected unexpected serious adverse reaction(s)
T2DM	type 2 diabetes mellitus
TEAE(s)	treatment-emergent adverse event(s)
$t_{½}$	terminal half-life
T_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
WHO	World Health Organization

DEFINITIONS OF TERMS

Electronic source system (eSource)	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a eCRF as determined by the protocol. Data in this system may be considered source documentation

1. INTRODUCTION

The prevalence of obesity is increasing worldwide. The World Health Organization (WHO) estimated that worldwide obesity has nearly tripled since 1975, affecting more than 650 million adults (WHO 2017). In the United States (US) in 2015-2016, 39.8% of adults and 18.5% of children and adolescents were obese, representing a significantly increasing trend compared to the prevalence of 30.5% and 13.9%, respectively, reported in the 1999-2000 period (Hales 2017). The US Centers for Disease Control and Prevention predict that obesity-related deaths could soon overtake smoking-related illnesses as the leading cause of mortality in the US. Indeed, obesity represents a major risk factor for cardiovascular (CV) diseases (eg, hypertension, atherosclerotic diseases, stroke), metabolic diseases (eg, type 2 diabetes mellitus [T2DM], dyslipidemia, non-alcoholic fatty liver disease [NAFLD]/ steatohepatitis [NASH]), conditions of the genito-urinary system (polycystic ovary syndrome, sexual dysfunction, stress urinary incontinence), musculoskeletal apparatus (eg, degenerative arthritis, pain). In addition, obesity is associated with impaired quality of life, an increased risk of depression, and several types of cancers, predominantly of the digestive tract and female reproductive system (Kyrgiou 2017; Wolfe 2017). The increased obesity-related morbidity was recently demonstrated in the Patient Outcome Research to Advance Learning study of more than 12 million individuals in the US who were overweight or had obesity and assessed for the prevalence of cardiometabolic risk factors: elevated blood pressure, elevated triglycerides, low high-density lipoprotein–cholesterol (HDL-C), and prediabetes. Compared with being overweight, obesity classes I (body mass index [BMI] 30.0-34.9 kg/m^2), II (BMI 35.0–39.9 kg/m^2), and III (BMI ≥40 kg/m^2) were associated with a nearly 2-fold, 3-fold, and 4-fold, respectively, greater probability of having at least 1 cardiometabolic risk factor (Nichols 2017). Hence, subjects with severe obesity (BMI >35 kg/m^2) are consequently more affected by the disease, have a poor quality of life, and thus have the greatest need for weight-loss therapy. Indeed, these comorbid conditions are expected to improve or go into remission in the presence of effective and sustained weight loss.

Current treatments for severe obesity include dietary and behavioral interventions, pharmacologic therapies, and eventually bariatric surgery. While combination strategies using diet, exercise, and behavior therapy have been shown to be more effective in the short term than diet and exercise alone (NIH 2000), these treatments are usually ineffective in subjects who are severely obese. Although weight reduction by as little as 5% of body weight has been shown to improve many obesity comorbidities, this modest weight reduction is insufficient to result in significant improvement in this population. Additionally, weight regain is common in severely obese patients, even when approaches are used that combine dietary therapy with exercise and behavior modification.

Pharmacotherapy is the second-line therapy recommended when lifestyle changes are ineffective in yielding significant weight loss. Currently available drug therapies include gastrointestinal (GI) lipase inhibitors such as orlistat (Xenical® [Xenical USPI], Roche Laboratories, Inc. or Alli®, GlaxoSmithKline Inc.), selective 5-HT_{2C}-receptor agonists such as lorcaserin (Belviq® [Belviq USPI], Arena Pharmaceuticals Inc.), glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide (Saxenda® [Saxenda USPI], Novo Nordisk Inc.), the combination of

naltrexone, an opioid antagonist, and bupropion, a dopamine and norepinephrine-reuptake-inhibitor (Contrave®, Mysimba®, Orexigen Therapeutics Ireland Ltd.), and the combination of phentermine, a sympathomimetic amine, and topiramate, an anti-epileptic drug (Qsymia® [Qsymia USPI] in the US, Vivus Inc.). In addition, phentermine (Adipex-P USPI), as well as some other anorectic agents (including diethylpropion, benzphetamine, and phendimetrazine), are registered in the US for short-term use (a few weeks, according to the label). Pharmacological compounds have variable efficacy and their use can be limited by side effects including diarrhea, abdominal cramps, and reduced absorption of fat-soluble vitamins with orlistat (Xenical USPI); serotonin-associated adverse reactions; cognitive impairment, psychiatric disorders, and possible valvular heart disease with lorcaserin (Belviq USPI); nausea, vomiting, elevation in pulse rate, and acute pancreatitis with liraglutide (Saxenda USPI); GI side effects, psychiatric, neurocognitive and sleep disorders with the combination of naltrexone and bupropion (Contrave USPI); and cognitive impairment, psychiatric disorders, and elevation in pulse rate with the combination of phentermine and topiramate (Qsymia USPI); and adverse events (AEs) related to the central nervous system or the cardiovascular system with phentermine (Adipex-P USPI).

Although bariatric surgery represents the most effective treatment option for severe obesity as it provides significant and sustained weight loss, and is more effective than lifestyle or pharmacological management in achieving glycemic control and reductions in morbidity and mortality, it can be associated with peri-operative (eg, venous thromboembolism, anastomotic leaks, wound infections, bleeding, and hernias) and post-operative (eg, nausea, vomiting, dumping syndrome, fat-soluble vitamin malabsorption) complications.

Given the above, there is a need for more effective and well-tolerated weight-management therapies that may also positively affect obesity-related comorbidities such as hypertension, dyslipidemia and T2DM (Padwal 2003).

While patients who undergo gastric banding and gastric bypass surgery have a reduction in caloric intake, there are also changes in several gut hormones that may play a role in reducing appetite and enhancing glucose control (le Roux 2007). Among the changes that have been consistently observed following bariatric surgery are increased postprandial levels of glucagon, GLP-1, and oxyntomodulin (OXM) (Chandarana 2012; le Roux 2007). Therefore, administration of metabolically stable endogenous gut peptides represents a potential therapeutic approach to modulating the pathophysiology of obesity and T2DM.

Oxyntomodulin is an endogenous 37-amino acid peptide secreted from enteroendocrine L-cells in the gut in response to and in proportion to nutrient ingestion. Oxyntomodulin is a dual agonist, acting at both the GLP-1R and the glucagon receptor (GCGR). These combined actions at the GLP-1R (enhanced glucose-stimulated insulin secretion and suppression of food intake) and the GCGR (suppression of food intake, increased energy expenditure, and improved lipid metabolism) suggest that OXM-based therapeutics could provide several benefits to obese patients and might produce superior weight loss as compared to currently available weight-management medications. Rodent and human studies support this hypothesis. Oxyntomodulin-based agonists cause marked weight loss in obese mice, and that effect is reduced in mice

lacking either GLP-1R or GCGR (Day 2009). Oxyntomodulin treatment in humans reduced food intake acutely by 14 to 20% (Cohen 2003; Field 2010) and resulted in a 2% body weight reduction after 4 weeks relative to subjects who received placebo (Wynne 2005).

JNJ-64565111 (efinopegdutide, formerly designated as HM12525A, developed by Hanmi Pharmaceuticals) is a synthetic, modified OXM peptide; it is the site-specific form of HMGLP/GCG25 (a GLP-1/glucagon dual agonist peptide), that is conjugated to constant region of human immunoglobulin G4 fragment (HMC001) via a 10 kDa polyethylene glycol (PEG) linker. The constant region of human immunoglobulin G4 fragment was chosen as the stabilizing agent, because it is a highly prevalent blood protein and has an in vivo half-life of several weeks, and lacks immune effector functions, such as complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity.

In vitro, JNJ-64565111 stimulates both GLP-1 and GCGR with comparable potency. Moreover, JNJ-64565111 lowers body weight and plasma glucose in animal models of obesity and T2DM. The mechanisms mediating body weight loss by JNJ-64565111 are thought to be via synergistic effects on caloric (food) intake and energy expenditure. In addition, the theoretical potential for blood glucose elevation with JNJ-64565111 due to GCGR agonism, appears to be efficiently offset by its GLP-1 receptor activity, as demonstrated by reduced blood glucose levels in mice and in humans with T2DM, as summarized in Section 1.1.1, Nonclinical Studies and 1.1.2, Clinical Studies with JNJ-64565111. JNJ-64565111 lowers cholesterol, low-density lipoprotein (LDL), and triglycerides in animal models of dyslipidemia.

For the most comprehensive nonclinical and clinical information regarding JNJ-64565111, refer to the latest version of the Investigator's Brochure for JNJ-64565111 (JNJ-64565111 IB).

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background on JNJ-64565111

1.1.1. Nonclinical Studies

Pharmacologic Profile

JNJ-64565111, formerly designated as HM12525A, is a site-specific conjugate of HMOXM25 (GLP 1/glucagon dual receptor agonist; also abbreviated to HMGLP/GCG25) and the HMC001 linked via 10 kDa polyethylene glycol (PEG) linker.

Simultaneous activation of GLP-1R and GCGR were shown to have beneficial effects in body weight loss by synergistic regulation mechanisms in energy intake and expenditure. Using a high-fat, diet-induced obese (DIO) animal model (ie, DIO mice), studies showed potent body weight loss by food intake inhibition as well as increased energy expenditure following treatment with JNJ-64565111. The body weight loss was mainly derived from the fat mass reduction, and accompanied with improvements in serum lipid profile. In addition, the simultaneous activity of JNJ-64565111 on GLP-1R and GCGR resulted in glucose-lowering in other animal models.

JNJ-64565111 normalized the glycemic excursion following an intraperitoneal glucose tolerance test in DIO mice and improved glycemic control in an animal model of T2DM (ie, db/db mice).

Safety Pharmacology

In safety pharmacology studies, JNJ-64565111 was evaluated in neurobehavioral, pulmonary, and cardiovascular pharmacology studies. In a neurobehavioral safety pharmacology study in rats up to 100 nmol/kg, JNJ-64565111 induced some changes (hunched posture, abnormal gait, reduce body temperature, tremor, etc.) but the changes were considered to be secondary to the large body weight losses recorded, which was an expected pharmacological effect. JNJ-64565111 produced no significant effects on any of the respiratory parameters (respiratory rate, tidal volume, and minute volume) measured in rats up to a dose of 100 nmol/kg. In cardiovascular safety pharmacology studies, JNJ-64565111 did not inhibit human ether-a-go-go-related gene (hERG) channel current in vitro even in 100-fold higher concentration (half maximal inhibitory concentration, IC_{50} >9.39 μM) than a pharmacological active concentration. In conscious telemetered cynomolgus monkeys, the pulse rate, Rautaharju corrected QT interval (QTcR) and body temperature generally remained within vehicle range except for the night periods where increases compared with vehicle control were observed at 15, 40, and 100 nmol/kg, but these changes remained within the high value limits of historical background data. Blood pressure values were generally lower than vehicle in the whole study period and may be consistent with the vasodilatory effects of GLP-agonists. In a subsequent cardiovascular safety pharmacology study in conscious telemetered cynomolgus monkeys given lower doses of 1 and 5 nmol/kg, there was no effect on body temperature, electrocardiogram (ECG) intervals (PR, QRS, QT, and QTcR), or blood pressure at either dose, and a slight non-adverse decrease in pulse rate during the nocturnal periods for the 1 nmol/kg dose was not evident at 5 nmol/kg. Overall, JNJ-64565111 was well tolerated across the battery of safety pharmacology studies.

Toxicology

The safety of JNJ-64565111 was addressed in several studies, including single- and repeat-dose studies of up to 24 weeks in rats and 16 weeks in monkeys. All safety studies, pivotal repeat-dose toxicity studies in rats and cynomolgus monkeys and genotoxicity studies were conducted in compliance with Good Laboratory Practices (GLP).

In general, JNJ-64565111 exposure increased with dose with no substantive sex differences in rat and monkey. Anti-drug antibodies (ADA) were produced in monkey but not in rats. The ADA decreased the exposure of JNJ-64565111 in the 16-week monkey toxicity study. There were no toxicological findings that resulted from antigen-antibody complex. No test-item related injection site lesion was observed in either the rat or monkey studies.

In all studies, reduced body weight and food consumption were dose-limiting in rats and monkeys, with the most common clinical signs in rats being hunched position, abnormal gait, and decreased activity.

Anemia characterized by decreased red blood cell count, hemoglobin, and hematocrit occurred in rats and monkeys, and these changes in red blood cell parameters were due to bone marrow damage consistent with malnutrition.

All organs changes observed in the rat 4-week toxicity study (0, 10, 30, and 60 nmol/kg/week) were attributed to effects caused by decreased food consumption, body weight loss and associated metabolic stress, not by a direct effect of JNJ-64565111. These included effects on liver, pancreas, intestine, bone and bone marrow, reproductive organs, and immune organs (thymus, etc.), and generally consisted of decreases in functional activity and organ size. The No Observed Adverse Effect Level (NOAEL) was 30 nmol/kg. At the NOAEL, Week 4 exposure in male and female rats corresponded to a maximum concentration (C_{max}) of 274 and 321 nmol/L, and an area under the curve in the interval 0–168 hours (AUC_{168hr}) of 34,558 and 39,971 h.nmol/L, respectively.

JNJ-64565111 was generally well tolerated in monkeys during the 4-week toxicity study (0, 15, 40, and 100 nmol/kg/week) with the predominant treatment-related effects (reduced food intake, body weight loss, and/or poor body weight gain) attributable to the pharmacological action of the test substance resulting in a number of secondary findings on the erythrocytic and clinical chemistry parameters, liver and pancreas. Increases in pulse rate and QTcR were considered to be within the historical background range for monkeys. Based on non-adverse but pharmacology-related changes up to high dose, the NOAEL in a 4-week toxicity study in monkeys was 100 nmol/kg. At the NOAEL, Week 4 exposure in male and female monkeys corresponded to a C_{max} of 1,099 and 742 nmol/L, and AUC_{168hr} of 100,151 and 64,142 h.nmol/L, respectively.

The findings attributed to secondary effects of decreased food consumption and body weight loss were more severe in rats than monkeys. The findings generally showed partial or complete recovery after a 2-week treatment-free period in both rats and monkeys. Monkeys presented only liver (increased or decreased glycogen content) and pancreatic changes (degranulation of acinar cells related to fasting effects, and increased cellularity). Increased pancreas cellularity has been observed for other GLP-1 agonists (eg, exenatide) and is considered a pharmacological effect.

No mutagenic effects were detected with JNJ-64565111 during in vitro and in vivo genotoxicity studies.

In conclusion, the majority of findings recorded in the toxicity studies in rat and monkey are considered to be secondary to decreased food consumption and the large body weight losses recorded, an expected pharmacological effect, and JNJ-64565111 was considered well tolerated.

1.1.2. Clinical Studies with JNJ-64565111

Clinical experience with JNJ-64565111 includes a first in human study (ie, HM-OXM-101) and two 4-week multiple ascending dose (MAD) studies (ie, 64565111EDI1001 and 64565111EDI1002).

The first in human study had a single ascending dose (SAD) part in healthy subjects (dose levels: 0.25, 0.5, 1.0, 2.0, and 4.0 nmol/kg) and a MAD part in subjects with T2DM (dose levels: 0.5, 1.0, 1.5, and 2.0 nmol/kg, administered once-weekly for 4 weeks).

The second MAD study, 64565111EDI1001, was conducted in subjects with T2DM and explored higher doses of JNJ-64565111 (2.5 and 3.0 nmol/kg). Results from this study showed non-dose-proportional PK data after repeated doses compared to data observed in the SAD portion of Study HM-OXM-101. Hence, an additional 4-week MAD study (64565111EDI1002) is being conducted to evaluate the full-dose range and PK profile. In this study, 4 groups of subjects with T2DM and treated with metformin have been dosed with 5.0, 10.0, 12.4, and 15.0 mg of JNJ-64565111, (approximately equivalent to the body weight-based doses of 1.0, 2.0, 2.5, and 3.0 nmol/kg, respectively, for a 90 kg individual, see Table 1) once-weekly for 4 weeks. Each group is to be composed of 8 subjects randomly assigned to JNJ-64565111 and 2 subjects randomly assigned to placebo. As of 01 February 2018, all subjects have completed treatment with study drug, but subjects in the 15 mg group are still in the post-treatment follow-up period. Since the study is still ongoing, the individual subjects' level safety data remain blinded and the group level efficacy results from this study described below are to be considered preliminary.

Table 1: Comparison of JNJ-64565111 Doses Used in Phase 1 Studies

Weight-based dose of 6456511 (nmol/kg)	0.5	1.0	1.5	2.0	2.5	3.0
Fixed dose of 64565111 (mg)	2.5	5.0	7.4	10.0	12.4	15.0

Pharmacokinetics

In the first 2 Phase 1 studies, JNJ-64565111 was administered using weight-adjusted doses. PK analyses from these studies showed that following single subcutaneous (SC) administration, JNJ-64565111 is slowly absorbed with time to maximum concentration (T_{max}) at approximately 4 to 6 days post-administration. The terminal half-life ($t_{1/2}$) of JNJ-64565111 is 7 to 8 days with an accumulation ratio of approximately 3 to 4 fold after repeated dosing.

PK parameters in the ongoing Study 64565111EDI1002, where the full range of JNJ-64565111 was studied using a fixed dose rather than weight-based dose showed that following the first dose of JNJ-64565111 of 5 to 15 mg, the mean (±SD) JNJ-64565111 C_{max} ranged from 0.259 (0.072) to 0.744 (0.22) µg/mL and the range for T_{max} was 2 to 7 days post-dose.

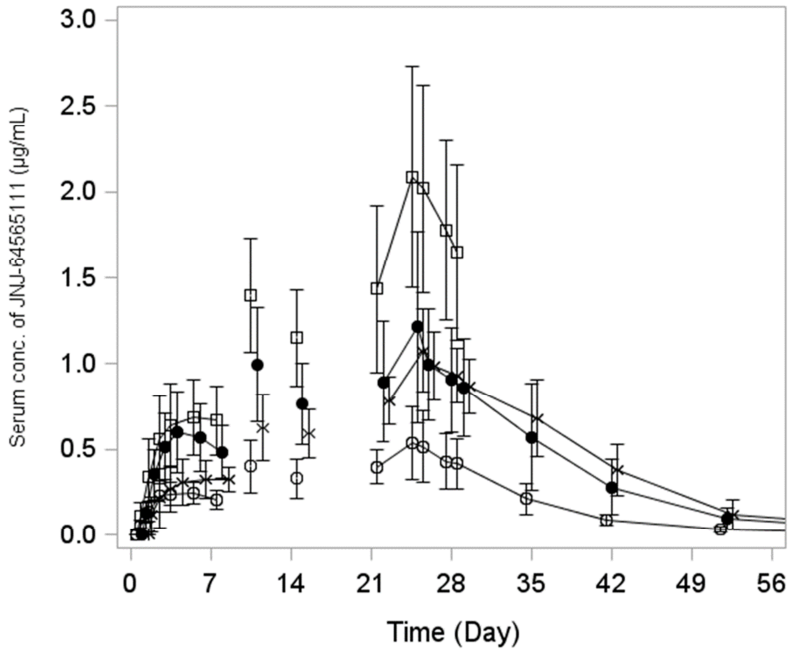
Following the last of the 4 weekly doses of JNJ-64565111 of 5 to 15 mg, the mean (±SD) JNJ-64565111 C_{max} ranged from 0.565 (0.20) µg/mL to 2.14 (0.66) µg/mL and the range of T_{max} was 0 to 6 days post-dose.

The mean accumulation ratio calculated as the ratio of Week 4 AUC_{τ} versus Week 1 AUC_{168h} was 2.33 to 4.01 for the 5 to 15 mg dose range, indicating moderate accumulation of JNJ-64565111 exposure upon multiple dosing that was commensurate with the dosing interval and t½ of JNJ-64565111 ($t_{½}$ = 6 to 7 days in Study 64565111EDI1002). The mean JNJ-64565111 trough serum concentrations on Days 8, 15, 22, and 29 (Figure 1) indicate that

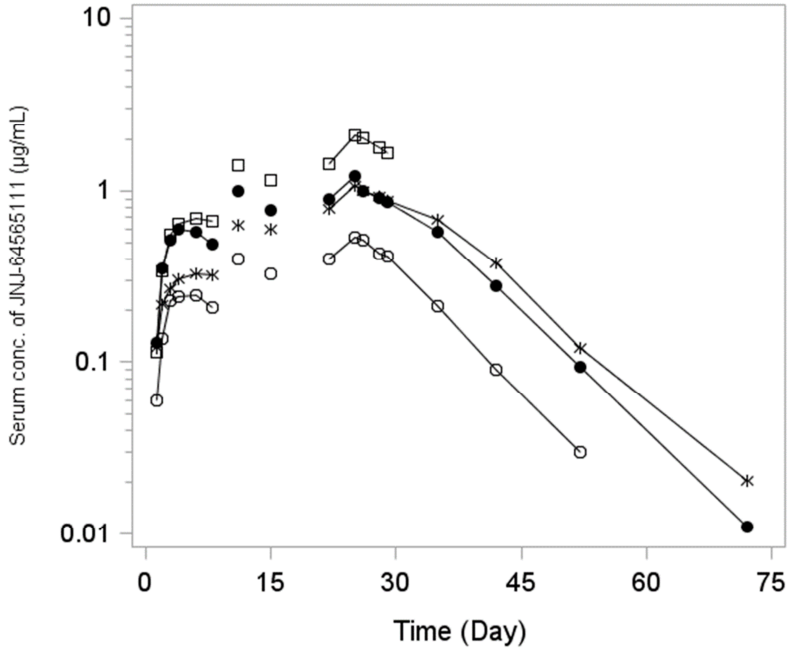
JNJ-64565111 had not attained steady-state following 4 weekly doses. This is also commensurate with the observed $t_{½}$ but >90% of steady-state was achieved by Week 4.

Figure 1: Mean (SD) Serum Concentration-time Profiles Following Multiple SC Administration of JNJ-64565111 Weekly for 4 Doses in T2DM Subjects

a. Linear-Linear



b. Log-Linear



Legend
○ 5.0 mg JNJ-64565111
● 10.0 mg JNJ-64565111
✳ 12.4 mg JNJ-64565111
□ 15.0 mg JNJ-64565111

Mean Week 1 and Week 4 C_{max} and AUC of JNJ-64565111, shown in Table 2, after the first and fourth dose increased for 5, 10, and 15 mg doses. However, the exposure from the 12.4 mg dose showed deviation from this behavior. The reason for the complex PK characteristics after administration of 12.4 mg dose in Study 64565111EDI1002 is currently not understood.

Table 2: Mean (Range) C_{max} and AUC of JNJ-64565111 on Weeks 1 and 4 (Study 645651111EDI1002)

Mean (Range)	Cohort 1 (5 mg)	Cohort 2 (10 mg)	Cohort 3 (12.4 mg)	Cohort 4 (15 mg)
C_{max} (µg/mL)				
Week 1	0.259 (0.155 – 0.373)	0.613 (0.367 – 0.920)	0.363 (0.233 – 0.579)	0.744 (0.321 – 1.01)
Week 4	0.565 (0.387 – 0.869)	1.23 (0.774 – 2.38)	1.09 (0.794 – 1.39)	2.14 (1.22 – 2.76)
AUC (µg·h/mL)				
Week 1	34.4 (19.0 – 48.6)	81.8 (49.2 – 121)	46.7 (25.4 – 77.7)	93.6 (36.4 – 136)
Week 4	79.2 (48.0 – 121)	182 (112 – 352)	160 (128 – 192)	307 (174 – 388)

AUC= area under the curve; C_{max}= maximum concentration.

Safety and Tolerability

Based on the completed and ongoing Phase 1 studies, treatment with JNJ-64565111 appears to be generally well tolerated. As with other GLP-1R agonists, the majority of the AEs were related to the GI system, with nausea, vomiting, abdominal distension, dyspepsia, and diarrhea being reported as the most common AEs. Of the non-GI AEs, the most common were decreased appetite and fatigue. No documented event of hypoglycemia has been reported. While there appeared to be a trend in dose-dependent increase in the incidence of AEs, most were mild in intensity. In general, no treatment-related or clinically relevant trends were observed for the hematology, coagulation, and biochemistry parameters, as well as for serum calcitonin, amylase and lipase values, and for the urinalysis parameters across dose groups. There were no clinically relevant changes in ECG parameters. None of the subjects in the completed Phase 1 studies that were treated with JNJ-64565111 experienced a SAE or discontinued due to AEs.

In the ongoing Study 64565111EDI1002, 2 SAEs occurred in the 10 mg/placebo group. Specifically, 1 subject who had low plasma sodium levels at baseline (132 mmol/L [132 mEq/L]), had a SAE of hyponatremia, (sodium levels of 114 mmol/L [114 mEq/L]), associated with mild hypokalemia and dehydration following protracted nausea, vomiting, and diarrhea, and which was treated with saline. The SAE occurred 4 days after the last dose of study drug and was considered to be related to study drug by the investigator. Laboratory and imaging workup for inappropriate antidiuretic hormone secretion (including brain on magnetic resonance imaging [MRI] and chest computed tomography [CT] scan to evaluate for central nervous system or pulmonary etiologies, respectively) were negative. The second SAE was influenza pneumonia that occurred 49 days after the last dose of study drug and was considered not related to study drug by the investigator. In addition, 3 subjects were withdrawn from the study due to AEs: 2 from Group 3 (12.4 mg/placebo) and 1 from Group 4 (15 mg/placebo). One subject in the 12.4 mg/placebo group had an AE of chest pain and ECG changes suggestive of ischemia on Day 8, after the first study drug dose. This event was considered not related to study drug by the

reporting investigator. Another subject in the 12.4 mg/placebo group withdrew consent on Day 22 (after receiving 3 doses of study drug) due to an AE of nausea. This event was considered related to study drug by the reporting investigator. There was no clinical, laboratory, or imaging evidence for pancreatitis or hepatobiliary pathology. In the 15 mg/placebo group, 1 subject discontinued on Day 22 (after receiving 3 doses) due to elevation in FPG (up to 24.42 mmol/L [440 mg/dL]) and hyponatremia and mild hypokalemia. The subject was treated with the addition of a sulfonylurea that rapidly improved FPG levels, with subsequent improvement in serum sodium. Both AEs were considered to be drug related by the investigators.

Pulse rate and blood pressure were assessed in all studies by use of ambulatory blood pressure monitoring (ABPM). In general, there was a consistent trend of increase in pulse rate and decrease in SBP and DBP across studies. In Study HM-OXM-101, following repeated doses, there was an increase in pulse rate after the 1.5 and 2 nmol/kg doses (LS means differences relative to placebo of 5.6 beats per minute [bpm] and 7.7 bpm, respectively). At the dose of 2 nmol/kg, SBP decreased by -7.8 mmHg (LS means differences relative to placebo). There was no consistent trend in changes in DBP.

In Study 64565111EDI1001, mean increases in pulse rate of 6.6 and 15.3 bpm were observed in the 2.5 and 3 nmol/kg groups, respectively, compared to a 1.3 bpm increase on placebo. Both SBP and DBP decreased by a mean of 11.8 and 4.2 mmHg, respectively, in the 2.5 nmol/kg group but remained unchanged in the 3 nmol/kg group and increased by 7.3 and 4.7 mmHg on placebo. A similar trend has been observed in the ongoing Study 64565111EDI1002 but individual treatment assignment is still blinded.

Efficacy

Body weight change

After 4 weeks of treatment in Study HM-OXM-101, a reduction in mean body weight was observed in all JNJ-64565111 groups while no changes in body weight were seen in subjects in the placebo group. Percentages of body weight loss were -1.3, -3.0, -4.1, and -3.9% in the 0.5, 1.0, 1.5, and 2.0 nmol/kg, respectively. In Study 64565111EDI1001, the 2.5 nmol/kg and 3.0 nmol/kg groups showed a mean body weight loss of -6.2% and -5.3%, respectively, relative to baseline compared to a mean weight loss of -1.4% in the placebo group. Weight loss was also observed in Study 64565111EDI1002, with decrease of approximately -4% in the 5, 10, and 12.4 mg group and approximately -6% in the 15 mg group compared to a decrease of approximately 1% in the placebo group.

Glycemic parameters

In Study HM-OXM-101, after 4 weeks of treatment, change in mean FPG from baseline of -1.62 mmol/L (-29.2 mg/dL), -0.64 mmol/L (-11.5 mg/dL), -2.21 mmol/L (-39.8 mg/dL), and -0.29 mmol/L (-5.2 mg/dL) were observed in the 0.5, 1.0, 1.5 nmol/kg, and placebo groups, respectively, compared to virtually no change in the 2.0 nmol/kg group. In Study 64565111EDI1001, the mean changes from baseline in FPG were 0.30 (5.4 mg/dL)

and -0.48 mmol/L (-8.7 mg/dL) in the 2.5 and 3.0 nmol/kg group, respectively, and -0.71 (-12.8 mg/dL) in placebo. In the ongoing Study 64565111EDI1002, in which the mean baseline HbA_{1c} was higher compared to the previous Phase 1 studies, hence resulting in a greater glucose variability, the mean changes in FPG were approximately -0.83 mmol/L (-15 mg/dL), 1.05 mmol/L (19 mg/dL), -0.67 mmol/L (-12 mg/dL), and 0.28 mmol/L (5 mg/dL) in the 5, 10, 12.4, and 15 mg groups, respectively, and -1.83 mmol/L (-33 mg/dL) in the placebo group. The median changes in FPG were approximately -1.22 mmol/L (-22 mg/dL), 0.56 mmol/L (10 mg/dL), -0.39 mmol/L (-7 mg/dL), -0.78 mmol/L (-14 mg/dL), and -2.0 mmol/L (-36 mg/dL) in the 5, 10, 12.4, 15 mg, and placebo groups, respectively.

After 4 weeks of treatment, mean HbA_{1c} values decreased from baseline in all groups in Study HM-OXM-101. Mean HbA_{1c} decreases from baseline were -0.19, -0.28, -0.73, -0.22, and -0.06 for the 0.5, 1.0, 1.5, and 2.0 nmol/kg groups and placebo, respectively. In Study 64565111EDI1001, mean HbA_{1c} decreases from baseline were -0.1% and -0.23% in the 2.5 nmol/kg and 3.0 nmol/kg groups, respectively, compared to an increase of 0.01% in the placebo group. In the ongoing Study 64565111EDI1002, HbA_{1c} reduction ranging from approximately -0.3 to -0.5% were observed in the 5 mg, 10 mg, 12.4 mg, and placebo group compared to an increase of approximately 0.3% in the 15 mg group.

Changes in fasting lipids

Across studies, 4 weeks of treatment with JNJ-64565111 was associated with decreases in mean values for total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides. The decreasing trend in these parameters was generally not observed in the placebo subjects. Compared to Study HM-OXM-101 where small decreases in high-density lipoprotein cholesterol (HDL-C) were observed in subject treated with JNJ-64565111, in Study 64565111EDI1001 and Study 64565111EDI1002, small decreases were observed with no apparent dose-dependency, ranging from -0.03 to -0.35 mmol/L (-1.2 to -13.7 mg/dL).

1.1.3. Ketogenesis with JNJ-64565111

An increase in ketones is a normal physiologic response to fasting, prolonged exercise, and certain dietary weight-loss regimens (eg, low carbohydrate-high fat diets) in which fatty acids are transformed in the liver into the ketones, aceto-acetate, and β-hydroxybutyrate. Physiologically, these ketones are used by the brain and muscles, including the heart, as an alternative fuel source when glucose is not readily available (Laffel 1999). The production of free fatty acids and their conversion to ketone bodies is stimulated by glucagon and inhibited by insulin. In the presence of near-normal or normal insulin function, such as in subjects without diabetes enrolled in this study, the rate of hepatic ketone formation is balanced by the rate of the body's ketones utilization and, to a certain degree, ketones loss into the urine. Importantly, in obese non-diabetic subjects who follow ketogenic diets, ketonemia *without acidemia* is commonly observed (Gomez-Arbelaez 2107).

As noted in Section 1.1.2, Clinical Studies with JNJ-64565111, treatment with JNJ-64565111 is associated with a percent reduction in body weight of up to approximately 6% from baseline (in part, related to reduced caloric intake) and mechanistically is an agonist for both GLP-1 and

GCGR. Therefore, as anticipated, a 2- to 3-fold increase in the serum levels of the ketone, β-hydroxybutyrate, relative to placebo was seen in the Phase 1 Studies 64565111EDI1001 and 64565111EDI1002 in which 50 subjects with T2DM (on either diet/exercise alone or on metformin monotherapy) were treated for 4 weeks with the addition of JNJ-64565111. Importantly, in these 2 studies conducted in subjects with T2DM, no AEs of ketoacidosis or metabolic acidosis were reported. In the current study of subjects without T2DM, serum β-hydroxybutyrate will be assessed as a marker of target engagement. To avoid the potential unblinding of subject to treatment assignment, both serum β-hydroxybutyrate and urinary ketones will remain masked to investigators and sponsor.

1.2. Comparator Drug – Liraglutide (Saxenda®)

Liraglutide is an acylated GLP-1 analogue that shares 97% amino acid sequence homology to human endogenous GLP-1 (7–37) (Saxenda USPI). The single amino acid substitution of lysine with arginine at position 34 and the attachment of a C16 fatty acid chain to lysine at position 26 enables liraglutide to self-associate and form a heptameric structure, which delays absorption from the SC injection site and provides protection against degradation by dipeptidyl peptidase (DPP)-IV enzyme and neutral endopeptidases. As a consequence, liraglutide has a much longer half-life than endogenous GLP-1 (~13 hr versus 1.5 to 2 min). Liraglutide binds to and activates the GLP-1R, in pancreatic beta cells (but not in pancreatic alpha cells) and is the target for endogenous GLP-1. This results in dose-dependent insulin release in patients with elevated glucose levels. At the same time, liraglutide acts in a glucose-dependent manner to decrease inappropriately high glucagon secretion, thereby blocking the effects of glucagon on hepatic glucose output. In addition to these glucoregulatory mechanisms of action in patients with T2DM, liraglutide slightly delays gastric emptying, and reduces body weight and body fat mass by reducing hunger and lowering energy intake.

The efficacy of once-daily SC liraglutide (titrated to 3.0 mg daily during a 4-week period), in conjunction with reduced caloric intake and increased physical activity in obese (BMI ≥30.0 kg/m^2) or overweight (BMI 27 to 29.9 kg/m^2 and at least 1 weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension) patients is well established, based on 3 large, multicenter, Phase 3 trials. Subcutaneous liraglutide (Saxenda®) 3.0 mg is approved in the US, Canada, European Union (EU), and other countries. It is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbid condition (eg, hypertension, T2DM, or dyslipidemia) (Saxenda USPI).

Liraglutide is administered SC once daily at any time of the day, without regard to the timing of meals. The initial starting dosage is 0.6 mg/day for 1 week; this low initial dosage is intended to reduce the risk of GI AEs. After 1 week, the dosage of liraglutide should be increased by 0.6 mg weekly until 3.0 mg/day dose is reached.

Liraglutide is generally well tolerated in non-diabetic obese and overweight subjects. In clinical trials, the most common adverse reactions, reported in ≥10% of obese and overweight patients treated with liraglutide 3.0 mg and more commonly than in patients treated with placebo, are: headache, nausea, diarrhea, constipation, vomiting, headache, decreased appetite, and dyspepsia.

Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and in patients with in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Liraglutide is also contraindicated in patients with a history of a serious hypersensitivity reaction to liraglutide, such as anaphylaxis or angioedema, and in pregnancy.

Local labels for liraglutide vary with regard to restrictions/contraindications, and therefore subjects with contraindications to the use of liraglutide based upon the local label of the investigational site will not be eligible to participate in the study.

For further information regarding liraglutide refer to the locally approved label (Saxenda USPI).

1.3. Overall Rationale of the Study

JNJ-64565111 has been studied in SAD and MAD studies in subjects with and without T2DM for up to a 4-week period. JNJ-64565111 was generally well tolerated and no safety signals precluding further development were seen. This Phase 2b dose-ranging study is being conducted to assess the safety and efficacy of JNJ-64565111 over a 26-week treatment phase in non-diabetic severely obese subjects and to provide information to select JNJ-64565111 dose(s) to be assessed in Phase 3 studies.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objectives

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with placebo after 26 weeks of treatment on:

- the percentage change in body weight from baseline
- safety and tolerability

Secondary Objectives

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with placebo after 26 weeks of treatment on:

- the proportion of subjects with ≥5% weight loss from baseline
- the proportion of subjects with ≥10% weight loss from baseline
- the absolute change in body weight from baseline

Exploratory Objectives

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with placebo after 26 weeks of treatment on:

- the change in BMI from baseline
- the change in waist circumference from baseline
- the change in fasting lipids (total cholesterol, LDL-C, HDL-C, and triglycerides) from baseline
- the change in FPG from baseline
- the change in fasting insulin from baseline
- the change in fasting C-peptide from baseline
- the changes in Homeostasis Model Assessment for B cell function (HOMA-B) and HOMA-insulin resistance (IR) from baseline
- the change in SBP from baseline
- the change in DBP from baseline
- the change in pulse rate from baseline
- the change in pulse-pressure product from baseline
- in a subset of subjects participating in the 24-hour ABPM assessment, the changes from baseline in 24-hour SBP, DBP, pulse rate, and pulse-pressure product
- PK exposure
- the change from baseline in scores on the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) (Kolotkin 2001; Kolotkin 2002), single item Ease of Weight Management, and Patient Activation Measure (PAM) (Hibbard 2005)
- in English-speaking subjects in selected countries only, the change from baseline in scores on the eating-related concept question (ERCQ) and the PROMIS physical function short form 8b (PROMIS SF 8b) (Note: the Patient Global Impression Status [PGIS] and Patient Global Impression of Change [PGIC] will be used to calculate responder definitions for the new instruments only and are not exploratory objectives.)
- in English-speaking subjects in selected countries only, describe pre-trial goals and expectations as well as post-trial experiences qualitatively using the Anticipations of Clinical Trial Treatment (ACTT) Pre-trial interviews and a modified Safety, Tolerability, and Efficacy Preview (STEP) exit interview

In non-diabetic severely obese subjects, to assess the effects of JNJ-64565111 compared with liraglutide after 26 weeks of treatment on:

- the absolute change and percentage change in body weight from baseline
- the proportion of subjects with ≥5% weight loss from baseline
- the proportion of subjects with ≥10% weight loss from baseline

2.2. Hypotheses

In non-diabetic severely obese subjects, treatment for 26 weeks with JNJ-64565111 compared with placebo leads to a greater:

Primary:

- percentage reduction in body weight from baseline

Secondary:

- proportion of subjects with ≥5% weight loss from baseline
- proportion of subjects with ≥10% weight loss from baseline
- absolute reduction in body weight from baseline

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled and open-label active-controlled, parallel-group, 5-arm, multicenter study. Non-diabetic, severely obese subjects who are ≥18 and ≤70 years of age and have a BMI ≥35 to ≤50 kg/m^2 will be assessed.

Subjects meeting all eligibility criteria will enter a 2-week run-in phase, which is to occur approximately 1 week after the screening visit and is designed to train the subject on SC self-injection and to establish the subject's ability to comply with the protocol-specified requirements. On Day 1, approximately 440 subjects who continue to meet eligibility criteria will be randomly assigned in a 1:1:2:2:2 ratio to blinded treatment with placebo, JNJ-64565111 (5.0, 7.4, or 10.0 mg) or open-label liraglutide, stratified by ABPM sub-study participation (yes or no), and then will enter a 26-week treatment phase. To maintain blinding, subjects randomly assigned to placebo will be subsequently randomly assigned in a 1:2:2 ratio to a placebo that matches the injection volume of the 5.0, 7.4, and 10.0 mg JNJ-64565111 doses (ie, 11, 22, and 22 subjects, respectively). Post-randomization visits will be conducted at Weeks 5, 10, 15, 20, 26/end-of-treatment (EOT) visit and 4-week SAE follow-up after Week 26/EOT visit. A subset of subjects in the ABPM sub-study will have 2 additional visits (ie, Pre-Day 1 and Pre-Week 26). A subset of subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample. All subjects will be contacted preferably by telephone to reinforce the adherence to diet and exercise, study drug dosing reminder, assessment of subjects' status, and compliance with the protocol procedures (eg, diary completion reminder) at Week 2. Study-site staff is encouraged to contact subjects (preferably by telephone) to do the same at some time in between Week 5, 10, 15, 20, and 26 visits. Subjects in the open-label liraglutide treatment group will also be contacted preferably by telephone at Weeks 1, 3, and 4 to remind about the dosing titration (ie, to increase their dose of liraglutide by an 0.6 mg dose increment weekly).

During the pre-treatment/run-in and treatment phases, subjects will undergo efficacy and safety assessments including physical examination, ECG, laboratory testing, and vital signs measurement. A serum pregnancy test will be performed at screening and Week 26/EOT in

women of childbearing potential. In a subset of subjects, a 24-hour ABPM (approximately 120 subjects total) will be performed.

Counseling should be done by dietitians/nutritionists on Day 1/Day of Randomization to provide assessment and recommendation on a reduced-calorie diet and exercise regimen (see Attachment 4). At subsequent visits (Week 5, Week 10, Week 15, and Week 20), counseling and reinforcement of the recommended diet and exercise regimen will be conducted by a trained counselor. At each treatment visit, the investigator or qualified, assigned designee will review the subject's diaries, concomitant medications, and the AEs that started or changed since the last visit.

The efficacy evaluation will include the percentage change in body weight from baseline as the primary efficacy endpoint.

Safety evaluations will include the monitoring of AEs (including protocol-specified AEs of interest), vital sign measurements, clinical laboratory tests (including calcitonin, lipase, amylase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin), urinalysis, review of concomitant medications, and serum pregnancy testing. Refer to Section 9.10, Safety Evaluations, for further details.

Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) and the 4-week SAE follow-up. Subjects that discontinue study drug early will continue in the study and be assessed with the off-treatment procedures at the subsequent visit(s) per the Time and Events visit schedule, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 26 visit. These off-treatment visits will include collection of SAEs, specific AEs of interest (ie, major adverse cardiovascular events [MACE] events, acute pancreatitis, and possible cases of thyroid neoplasm), vital signs (including body weight), and concomitant medications (see Section 9.4.5, End-of-Treatment/Early Study Drug Discontinuation). Subjects who discontinued prior to Week 26 and have the 4-week SAE follow-up visit after last study drug dose, do not need to return for a second 4-week SAE follow-up visit. All subjects (except those who died, were lost to follow-up, or have a withdrawn consent) will have a follow-up visit approximately 5 weeks after the last dose of study drug for JNJ-64565111-treated or placebo-treated subjects and 4 weeks after the last dose of study drug for liraglutide-treated subjects to collect any SAEs. For subjects randomly assigned to JNJ-64565111 or placebo, blood samples for immunogenicity ADA and PK assessments will also be obtained at this SAE follow-up visit.

A 24-hour ABPM assessment will be performed at selected sites and will involve approximately 120 subjects (approximately 15 subjects each in the placebo and JNJ-64565111 5 mg groups, and 30 subjects each in the JNJ-64565111 7.4 mg, JNJ-64565111 10 mg, and liraglutide groups). During the run-in phase, these subjects will wear the ABPM device for at least 22 hours 1 or 2 days prior to the Day1/Randomization visit. The ABPM readings will be masked. When subjects return for the Day 1 visit, ABPM readings will be assessed for subjects' eligibility into the ABPM sub-study based on the ABPM requirements (see Section 4.1, Inclusion Criteria, for

further details). After randomization, subjects participating in the ABPM assessment will be required to repeat a 24-hour ABPM assessment 1 or 2 days prior to the Week 26/ EOT in subjects who have not withdrawn consent or died. For subjects treated with JNJ-64565111 or matching placebo, every effort should be made to have the procedure performed within 7 days from the previous dose of study drug.

The IWQOL-Lite, Ease of Weight Management, and PAM will be administered at all sites to all subjects. The PROMIS SF 8b and ERCQ along with both the PGIS and PGIC will be administered at selected sites and will involve approximately 120 English-speaking subjects. These instruments are intended to measure eating-related concepts such as hunger, appetite, cravings, and satiety, and physical function.

Subjects who withdraw from the study will not be replaced.

An interim analysis will be performed when approximately 90% of subjects have either completed or discontinued prior to approximately 10 weeks of study drug treatment. The objective of this interim analysis is to identify active treatment groups, if any, associated with safety or tolerability issues and to facilitate planning of the Phase 3 program. The dissemination of the interim analysis results will be limited to an internal data monitoring committee (DMC), and will not be shared with investigators, subjects, or the sponsor staff who will continue to be involved in the conduct of the study before the final database lock. The operational details of the interim analysis will be provided in the DMC Statistical Analysis Plan (SAP) (see Section 11.7, Interim Analysis).

The overall study duration is approximately 33 weeks and comprises of 3 phases:

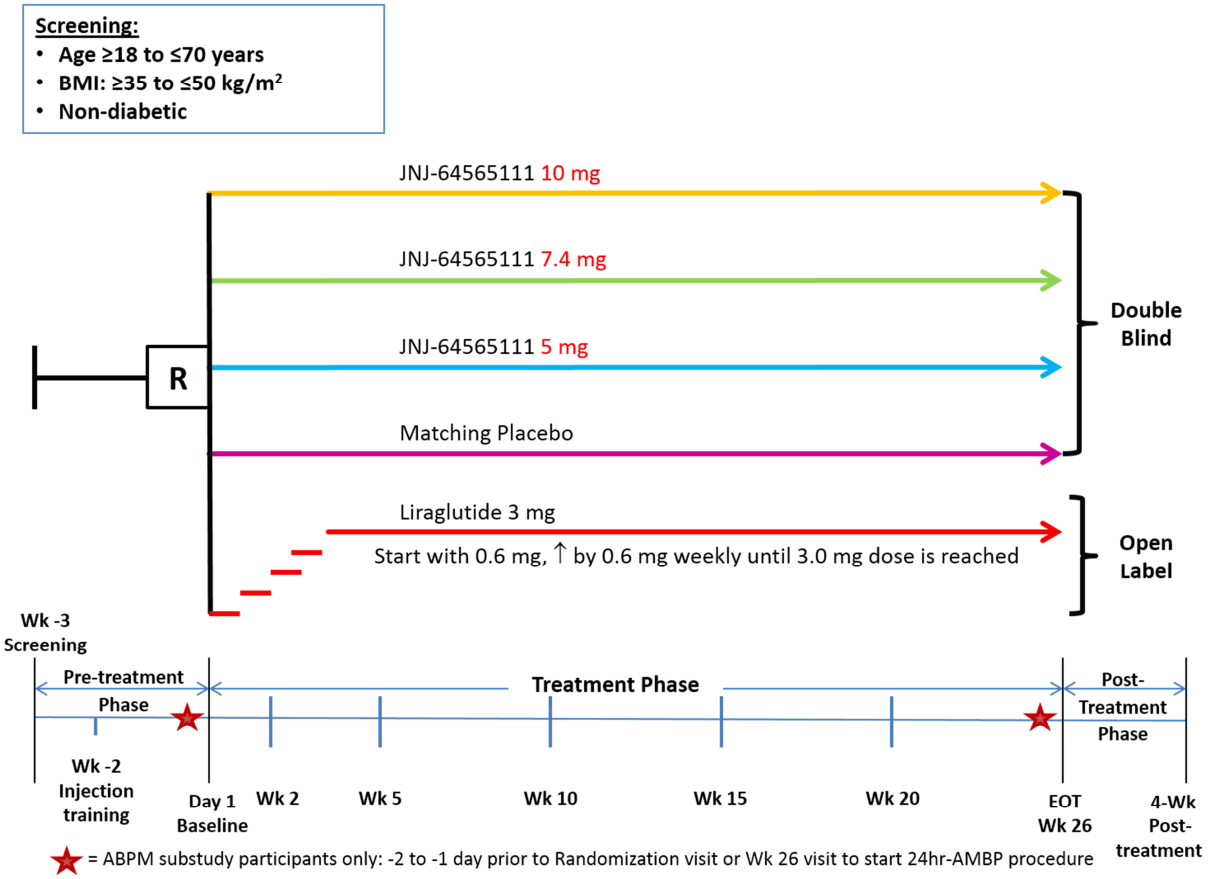
- Pre-treatment phase
  - Screening phase: 1 week
  - Run-in (injection-training) phase: 2 weeks
- Treatment phase (double-blind and open-label arms)
  - Placebo- and active-controlled treatment phase: 26 weeks
- Post-treatment phase (SAE follow-up visit): 4 weeks

Approximately 440 subjects will be randomly assigned in a 1:1:2:2:2 ratio to one of the following once-weekly SC treatments:

- 55 subjects to double-blind placebo matching JNJ-64565111
- 55 subjects to double-blind JNJ-64565111 5.0 mg
- 110 subjects to double-blind JNJ-64565111 7.4 mg
- 110 subjects to double-blind JNJ-64565111 10.0 mg
- 110 subjects to open-label liraglutide 3.0 mg

A diagram of the study design is provided in Figure 2.

Figure 2: Schematic Overview of the Study



3.2. Study Design Rationale

The study was designed in general accordance with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance on the development of medications and clinical investigations for the treatment of obesity (FDA 2009; Guidance for Industry Developing Products for Weight Management 2007; Guideline on Clinical Investigation of Medicinal Products Used in Weight Management 2016).

Blinding, Study Phases, Treatment Groups

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used in the JNJ-64565111 and placebo treatment arms to reduce potential bias during data collection and evaluation of clinical endpoints. Due to the use of commercially available liraglutide, which is provided as pre-filled auto-injector pens and must be injected daily, it is not practical to double-blind the liraglutide treatment arm.

The 1-week screening phase will allow time prior to the beginning of the injection-training phase to obtain laboratory results that are needed to determine the subject's eligibility for the study. Subjects enrolled in this study will likely have no prior experience with self-injection of medication. Therefore, a 2-week SC injection-training phase will include training of subjects by the study staff on the use of the pre-filled safety injectors for self-injection. Study staff will also evaluate the subject's ability and willingness to self-inject prior to being randomized. The duration of the treatment phase in this study is 26 weeks, which should be sufficient to capture the maximal or near-maximal weight loss effects of the active doses. The 4-week SAE follow-up visit is designed to assess safety by collecting data on SAEs or resolution of ongoing SAEs that occurred since the last study visit.

Study Population

The randomized study population consists of non-diabetic severely obese subjects, ages 18 to 70 years, inclusive, at screening who have a BMI ≥35 kg/m^2 to ≤50 kg/m^2. Men and women will be enrolled in this study. In this study the definition of "severe" obesity, which is commonly used within the surgical community to refer to subjects who are eligible for bariatric surgery, is inclusive of the WHO definition of Obese Class II (35-39 kg/m^2) and III (≥40 kg/m^2) (WHO 2017).

Dose Selection and Dose Interval of JNJ-64565111

The t ½ of 6 to 8 days allows for a weekly dosing frequency for JNJ-64565111. While in earlier Phase 1 studies, JNJ-64565111 was administered using weight-based doses, fixed doses of JNJ-64565111 were tested in Study 64565111EDI1002. As such, the dosing regimen is more practical and is likely to be associated with greater adherence. Fixed weekly doses of 5 and 10 mg of JNJ-64565111 in the Phase 1 Study 64565111EDI1002 showed similar exposures compared with doses of 1.0 and 2.0 nmol/kg/week observed in the previous Phase 1 MAD study. Moreover, fixed dosing resulted in overall similar variability in exposure compared with body weight-based dosing for equivalent doses of 5 and 10 mg of JNJ-64565111. In 4-week studies in overweight and obese subjects with T2DM, doses of JNJ-64565111 in this dose range resulted in approximately 2 to 4% reduction in body weight. As this duration of treatment is too short to observe the full weight-loss potential of any pharmacological intervention, this study is being conducted with the doses specified for 26 weeks of treatment. Twenty-six weeks is generally sufficient to capture the maximal or near-maximal weight loss in a Phase 2 trial. The lower dose of 5 mg was chosen since it is expected to be a minimally efficacious dose. The upper end of the dose range was selected because drug exposures are highly variable beyond doses of 10 mg weekly (Study 64565111EDI1002) and because doses above 10 mg, while leading to greater weight loss, also appeared to be less tolerated as indicated by a dose-dependent increase in the incidence in GI AEs as well as increase in mean pulse rate. As the assessment of more than 2 active doses is desirable to evaluate a dose-response relationship for JNJ-64565111 an intermediate dose of 7.4 mg was incorporated into the current study.

Choice of Efficacy Measures

The primary efficacy endpoint will be a comparison of percentage change in body weight between the JNJ-64565111-treated and placebo-treated groups. This is an accepted endpoint for clinical trials of weight-management products (FDA 2009). Secondary endpoints will include the proportion of subjects in each treatment group who lose ≥5% and ≥10% of baseline body weight and the mean absolute change in body weight, both of which are also accepted endpoints in weight-management studies.

Change from baseline in SBP, DBP, pulse rate, pulse-pressure product, and fasting lipid levels will be evaluated to assess the effects of JNJ-64565111 on the common weight-related comorbidities of hypertension and dyslipidemia. Additional exploratory measures of efficacy (ie, change from baseline in BMI; waist circumference; FPG, fasting insulin, and fasting C-peptide; serum β-hydroxybutyrate; IWQOL-Lite, single item Generic Rating of Health, single item Ease of Weight Management, PAM, and in English-speaking subjects in selected countries only, ERCQ, PROMIS SF 8b, a ACTT pre-trial interview, and a modified STEP exit interview) will be evaluated to identify additional treatment effects of JNJ-64565111.

Rationale for Use of Placebo Control

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment, improving the precision of the assessments of both efficacy and safety. A study without a placebo arm cannot properly determine the weight-reducing efficacy of a weight-management product, given the impact of co-interventions (eg, diet and exercise counseling). Similarly, given background occurrence of AEs in this population in which comorbidities are common, without a placebo treatment group, it is not possible to precisely define the safety and tolerability profile of a new weight-management product.

Rationale for Open-label Reference Arm

Liraglutide is a GLP-1 receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbid condition (eg, hypertension, T2DM, or dyslipidemia), as indicated in the product labeling. In a Phase 3 clinical study of 56 weeks duration with 3.0 mg liraglutide conducted in obese and overweight subjects the mean change in body weight was -4.5% (95% confidence interval [CI]: -3.8 to -5.2%) relative to placebo control. Given the partially common mechanism of action, a direct comparison between liraglutide and JNJ-64565111 will facilitate the interpretation of efficacy findings and of possible differences in efficacy measures observed between the 2 drugs. Importantly, the use of liraglutide will provide an essential reference arm for the assessment of the safety and tolerability profile of JNJ-64565111, as it is expected that both agents are associated with an increased incidence of GI AEs. Further, the same administration route SC reduces the possible confounding effect of treatment compliance that would exist if the comparator was an oral agent.

Choice of Patient-reported Outcome (PRO) Measures and Subject Interviews

Evaluation of health status and treatment experience from the subject's perspective is increasingly important in the evaluation of new treatments. Several PRO instruments have been selected to measure these concepts of importance (ie, IWQOL-Lite, Ease of Weight Management, PAM). In English-speaking subjects in selected countries only, PRO instruments will also be administered to measure eating-related concepts of hunger, appetite, cravings, satiety, and physical function (ie, PROMIS SF 8b, ERCQ, PGIS, and PGIC). Also, in a subset of subjects, interviews will be conducted to describe qualitatively pre-trial goals and expectations as well as post-trial experiences. The ACTT pre-trial interview and a modified STEP exit interview will be used (see Section 9.7.3, Patient-reported Outcomes for a full description of the objectives of the PRO measures). The exploratory endpoints from this subset of subjects may be used to support outcomes/benefits from a subject's perspective.

Interim Analysis

An interim analysis will be performed when approximately 90% of subjects have either completed or discontinued prior to 10 weeks of study drug treatment. The objective of this interim analysis is to identify active treatment groups, if any, associated with safety or tolerability issues and to facilitate planning of the Phase 3 program. The dissemination of the interim analysis results will be limited to an internal DMC, and will not be shared with investigators, subjects, or the sponsor staff who are involved in the conduct of the study before the final database lock. The operational details of the interim analysis will be provided in the charter of the interim analysis committee.

Collection of Additional Information for Selected Adverse Events

For selected AEs of interest, investigators will be asked to provide additional information which may include the use of subjects' source documentation or supplementary electronic case report forms (eCRFs) to support more detailed analyses. These events include hypotension-related AEs, calcitonin elevation, acute pancreatitis, and thyroid neoplasm.

Pharmacokinetic Samples

Pharmacokinetics will be evaluated to explore exposure-response relationships, and to develop a population PK model. All PK data from subjects in this study will be combined with data from other clinical studies of JNJ-64565111 for a pooled population PK analysis to develop a structural PK model of JNJ-64565111, and to evaluate the dependence of the PK of JNJ-64565111 on population covariates.

Archive Samples for Exploratory Research

Numerous bio-markers have been studied as potentially important surrogate measures of cardiovascular and overall health of subjects (Ridker 2004). Plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for the analysis of important bio-markers (not prespecified) that could help to further explain and examine the efficacy and safety findings in this study.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Protocol inclusion/exclusion waivers are not permitted.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Subjects must have signed an informed consent form (ICF) indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
2. Male or female, 18 to 70 years of age, inclusive
3. BMI ≥35 to ≤50 kg/m^2 at the screening visit
4. Stable weight (ie, change of ≤5% within 12 weeks before screening based on medical history)
5. Subjects are, in the investigator's opinion, well-motivated, capable, and willing to learn how to self-inject treatment, as required for this study
6. On Day 1, subjects must have 100% compliance with the open-label placebo run-in medication based on 1 of the following:

   returned empty study drug cartons
   injections recorded in study drug diary
7. Women must be either:

   - postmenopausal, defined as:
     - >45 years of age with amenorrhea for at least 18 months, or
     - >45 years of age with amenorrhea for at least 6 months and <18 months and a serum follicle-stimulating hormone (FSH) level >40 mIU/mL (>40 IU/L), or
   - permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy, or
   - heterosexually active and practicing a highly effective method of birth control (failure rate of <1% per year when used consistently and correctly), including combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral, injectable, or implantable; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner (provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed; if not, additional highly effective method of contraception should be used), and agrees to remain on a highly effective method of contraception throughout the study and for at least 4 weeks after the last dose of study drug

Note: Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

- not heterosexually active

  Note: Women who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study and for at least 4 weeks after the last dose of study drug

8. Woman of childbearing potential (ie, those subjects who do not meet the postmenopausal definition in the Inclusion Criterion above, regardless of age) must have a negative highly sensitive serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening
9. Willing and able to adhere to the prohibitions and restrictions specified in this protocol

For Subjects Participating in the 24-hour ABPM Sub-study:

10. Subject understands instructions on the use of the ABPM device and is willing to undergo the 24-hour ABPM procedure
11. An average of 3 seated blood pressure readings of SBP >90 to <140 mmHg
12. Has completed a successful ABPM reading, defined as at least 22 hours of recording with ≥70% of valid scheduled readings, and no continuous interruption of >2 hours of recording

    Note: If the subject does not have a valid baseline ABPM reading according to the definition above or the subject has unexpected illness or other circumstance during the day(s) of the 24-hour ABPM recording that could confound the assessment of the endpoint, at the discretion of the investigator the subject may repeat the procedure within one week prior to randomizing subject to first study dose. If the invalid reading was due to subject noncompliance with the procedure, it is up to the investigator's discretion to decide whether the subject should attempt a second 24-hour ABPM procedure. If the 24-hour repeat recording is successful, this repeat recording will be used as the subject's baseline 24-hour ABPM. If no valid ABPM reading is obtained following the second attempt, the subject should be excluded from the ABPM sub-study, but may be randomized into the main study if they continue to meet other eligibility criteria.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

Metabolic/Endocrine

1. History of obesity with a known secondary cause (eg, Cushing's disease/syndrome)
2. History of Type 1 diabetes mellitus, T2DM, diabetic ketoacidosis (DKA), pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
3. Has an HbA1c of ≥6.5% or FPG ≥126 mg/dL (≥7.0 mmol/L) at screening

   Note: a one-time repeat measurement is allowed, at the discretion of the investigator, if the value of HbA_{1c} and/or FPG is not consistent with prior values

4. Ongoing, inadequately controlled thyroid disorder as assessed by the investigator's review of the subject's medical history. Subjects taking thyroid hormone replacement therapy must be on stable doses for at least 6 weeks before the screening visit
5. History of glucagonoma
6. Screening calcitonin of ≥50 pg/mL (≥50 ng/L), personal history or family history of medullary thyroid cancer, or of MEN 2, regardless of time prior to screening

   Note: Investigators are recommended to refer subjects with screening calcitonin value of ≥50 pg/mL (≥50 ng/L) to an endocrinologist for follow-up.

Cardiovascular

7. A myocardial infarction (MI), unstable angina, revascularization procedure (eg, stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before screening, or a revascularization procedure is planned during the trial
8. Heart failure of New York Heart Association (NYHA) Class II-IV cardiac disease (The Criteria Committee of the NYHA) (refer to Attachment 1, NYHA Classification of Cardiac Disease)
9. Findings on 12-lead electrocardiogram (ECG) at the screening visit that would require urgent diagnostic evaluation or intervention
10. An average of 3 seated blood pressure readings of SBP ≥160 mm Hg and/or DBP ≥100 mm Hg at the screening visit (refer to Attachment 2, Method of Blood Pressure and Pulse Rate Measurement)
11. History of tachyarrhythmia (eg, atrial flutter, atrial fibrillation, ventricular tachycardia) within 6 months before screening
12. An average of 3 seated pulse rate readings of <50 or >100 bpm

Gastrointestinal

13. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis)
14. History of acute or chronic pancreatitis
15. History of bariatric surgical procedure or a known clinically significant gastric emptying abnormality (eg, severe gastroparesis or gastric outlet obstruction)

Psychiatric-Related

16. History of a clinically significant eating disorder (eg, anorexia nervosa, bulimia, or binge-eating)
17. Any history of major depressive disorder within the last 2 years.
18. Any history of other severe psychiatric disorders (eg, schizophrenia, bipolar disorder, etc.).
19. Any lifetime history of suicide attempt.

Laboratory

20. Estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula at screening (Levey 2009), refer to Attachment 5, Clinical Laboratory Tests

    Note: A one-time repeat measurement is allowed at the discretion of the investigator, if the value for eGFR is not consistent with recent values

21. Alanine aminotransferase level is >2.0 times the ULN or total bilirubin is >1.5X the ULN (unless consistent with history of Gilbert's disease) at screening

    Note: A one-time repeat of ALT is allowed at the discretion of the investigator, if the screening value is not consistent with recent values.

22. Fasting triglycerides ≥600 mg/dL (≥6.77 mmol/L) at screening (or subsequent visit prior to randomization, if not fasting at screening).

    Note: A one-time repeat of the serum triglycerides is allowed, at the discretion of the investigator, if the screening value is not consistent with recent values.

23. Serum sodium < 130 mEq/L (<130 mmol/L)

Other Conditions

24. History of malignancy within 5 years before screening (eg, any evidence of active disease within 5 years, or diagnosis of malignancy within this period)

    Note: Subjects with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, are considered cured with minimal risk of recurrence, may participate.

25. Previous (ie, within 12 weeks from screening visit) or current use of a Highly Active Anti-retroviral therapy (HAART)

26. Major surgery (eg, requiring general anesthesia) within 12 weeks before screening, or has not fully recovered from surgery, or planned major surgery during the participation of the current study.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

27. Clinically important hematologic disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia) or a disorder of hemoglobin (ie, a hemoglobinopathy)

Medications/Therapies

28. Previous or current participation in a JNJ-64565111 study
29. Known allergies, hypersensitivity, contraindication, or intolerance to the excipients of JNJ-64565111 or liraglutide

30. Known or potential history of intolerance to prior use of any GLP-1 receptor agonist (eg, AEs, lack of efficacy) which, in the opinion of the investigator, makes participation not in the best interest of the subject
31. Currently treated with antihypertensive or antihyperlipidemic therapy that is not on stable dose for at least 4 weeks prior to screening

    Note: If during the screening phase adjustments to the antihypertensive or antihyperlipidemic medication regimen are considered to be clinically necessary, the subject should be excluded from continuing in the study. The subject may be rescreened after adjustments in the antihypertensive or antihyperlipidemic medication regimen have been made and the dose has been stable for at least 4 weeks.

32. Prescription weight-management medication (including but not limited to orlistat, topiramate and/or phentermine, lorcaserin, naltrexone and/or bupropion, or over-the-counter weight-loss medications or therapies within 12 weeks before the screening visit or is planning to initiate non-study-related weight-loss treatment during the study
33. Current or previous use of liraglutide within 12 weeks prior to the screening visit
34. Use of systemic corticosteroid medication within 12 weeks before the screening visit or likely to require treatment with systemic corticosteroid medication during study treatment phase (for longer than 2 consecutive weeks in duration)

    Note: Subjects using inhaled, intranasal, intra-articular, or topical corticosteroids or corticosteroids in therapeutic replacement doses may participate

35. Use of the following medications within the 12 weeks before screening or likely to require treatment with the following medications during study treatment phase:
    - Antihyperglycemic agents
    - Antipsychotic drugs
    - Anticonvulsants, including barbiturates, gamma-aminobutyric acid (GABA) analogues, hydantoins, phenyltriazines, succinimides, valproic acid and its derivatives, carbamazepine, zonisamide, and felbamate
    - Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists
36. Use of selective serotonin reuptake inhibitors (including but not limited to fluoxetine, sertraline, paroxetine, escitalopram, citalopram, dapoxetine, seproxetine, zimelidine, mesembrine, reboxetine) and serotonin-norepinephrine reuptake inhibitors (including but not limited to venlafaxine, duloxetine, desvenlafaxine, milnacipran, fluvoxamine) that have not been stable for at least 12 weeks prior to the screening visit
37. Received an investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks prior to screening

General

38. Significant change in smoking habits within 12 weeks before the screening visit
39. Female subject is pregnant or breastfeeding, planning to become pregnant during the study or follow-up phase, or planning to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study or for a period of 4 weeks after the last dose of study drug

40. An employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or is a family members of an employee or the investigator
41. Any condition that, in the opinion of the investigator or sponsor's medical monitor, would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments

For Subjects Participating in the 24-hour ABPM Sub-study

42. Currently treated with beta-blockers drugs or calcium-channel blockers
43. Currently has a pacemaker or automated implantable cardioverter defibrillator
44. Currently employed at a job that requires rotating or permanent night shifts

Investigators should ensure that all study eligibility criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the eligibility criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Women of childbearing potential who are heterosexually active, must remain on a highly effective method of birth control (failure rate of <1% per year when used consistently and correctly; refer to Section 4.1, Inclusion Criteria) throughout the study and for at least 4 weeks after the last dose of study drug.
2. Women must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 4 weeks after the last dose of study drug
3. Prohibited medications as detailed in Section 8, Pre-study and Concomitant Therapy.

4.4. Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened 1 time if the reason for non-eligibility relates to duration of stable thyroid hormone replacement, antihypertensive, or antihyperlipidemic therapy, or time from a MI, unstable angina, revascularization procedure or cerebrovascular accident. Subjects who are to be rescreened must sign a new informed consent before rescreening.

Subjects rescreened within 4 weeks may use the initial screening laboratory results to determine eligibility (with the exception of serum chemistry which must meet inclusion criteria range at Week -1 or within 3 weeks before Week -1). Rescreening for an abnormal laboratory value is only allowed as indicated for the specific laboratory exclusion (see Section 4.2, Exclusion Criteria).

5. TREATMENT ALLOCATION AND BLINDING

Randomization and Blinding Procedures

On Day 1, subjects will be randomly assigned to 1 of 5 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will use randomly permuted blocks. In addition, to assure maintenance of the randomization ratio in the ABPM sub-study, subjects will be stratified in the interactive web response system (IWRS) by participation in the 24-hour ABPM sub-study (yes or no). Subject enrollment into the ABPM sub-study at selected study sites will be tracked and capped as necessary. If the overall study target enrollment has been achieved, subject recruitment may be closed even if the target enrollment numbers for the ABPM sub-study have not been reached.

At baseline (Day 1), the treatment code, which is linked to the randomization schedule, will be assigned after logging on to the IWRS designated by the sponsor. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. As subjects are randomly assigned to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New study drug kits will be assigned each time the IWRS is accessed for dispensing additional study drug.

Blinding

Liraglutide will be administered in an open-label fashion in this study.

JNJ-64565111 and placebo will be given in a double-blind fashion, as described below. To maintain blinding, subjects randomly assigned to placebo will be subsequently randomized to receive the corresponding volumes of placebo matching the 5.0, 7.4, and 10.0 mg JNJ-64565111 doses.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the JNJ-64565111 treatment assignment (eg, serum β-hydroxybutyrate, urine ketones, and ABPM measurement) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the

treatment by accessing the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site (except as necessary for the clinical management of the subject) or sponsor personnel.

In general, treatment codes will be disclosed fully only after the study is completed and the clinical database is closed. However, for the specified interim analysis, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

6. DOSAGE AND ADMINISTRATION

6.1. Pre-Randomization Open-label Placebo

At the Week -2 visit, subjects will be instructed on the use of pre-filled safety injectors to perform SC self-injections, and will be asked to perform a self-injection in the presence of the study-site staff. Only subjects who express willingness and demonstrate the ability to administer SC injections are eligible to participate in the study (see Section 4.1, Inclusion Criteria, No. 5). To assess compliance with the dosing regimen, eligible subjects will be dispensed pre-filled safety injectors containing 0.5 mL open-label placebo and instructed to perform once-weekly self-injections at home during the 2-week run-in phase, as well as keep a study drug diary of their injection schedule (see Section 9.3.2.1, Training on Subcutaneous Drug Administration for details on training instructions).

6.2. Post-Randomization Double-blind JNJ-64565111 or Matching Placebo and Open-label Liraglutide

Double-blind JNJ-64565111 or Matching Placebo

JNJ-64565111 will be supplied as a solution for injection at a concentration of 20.0 mg/mL. Blinded study drug will be provided in pre-filled safety injectors with attached SC needle, pre-filled with nominal volumes of 0.25, 0.37, or 0.50 mL of JNJ-64565111 (5.0, 7.4, and 10.0 mg, respectively) or 1 of 3 matching volumes of placebo.

On Day 1, subjects randomly assigned to the double-blind treatment arms will receive a supply of their randomly assigned study drug (or matching placebo), and will be reminded of the once-weekly dosing regimen and to record the date and time of each administered dose in the study drug diary. Subjects will self-administer the first dose of JNJ-64565111 or matching placebo at the site under the supervision of study staff.

Subjects will be reminded that if the day of their once-weekly injection coincides with the day of a clinic visit, subjects are not to inject JNJ-64565111 or matching placebo before arriving at the clinic; once all study visit procedures have been completed, subjects may self-administer blinded study drug (or matching placebo) either at the study site or once they have returned home that day.

JNJ-64565111 or matching placebo will not be titrated. Subjects will remain on their assigned dosages throughout the treatment phase (ie, until Week 26 or early discontinuation of study drug).

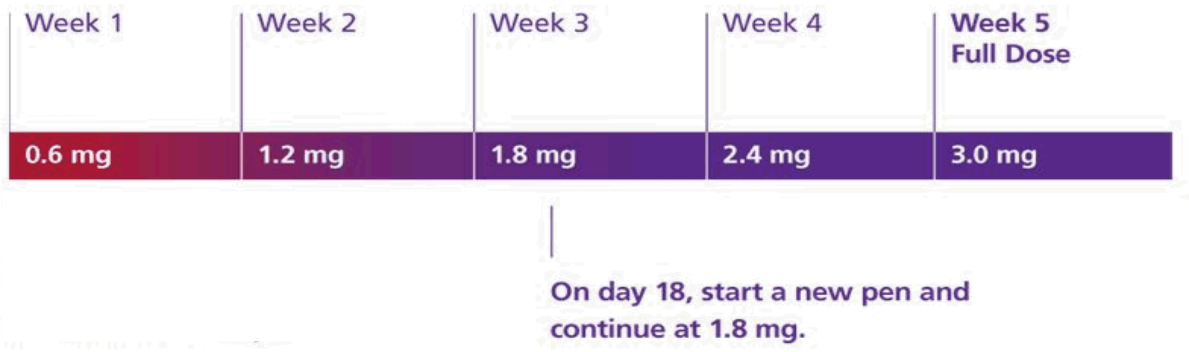
Open-label Liraglutide (Saxenda®)

Commercially available supplies of liraglutide will be dispensed to subjects randomly assigned to the open-label liraglutide arm of the study. Liraglutide is supplied as a pre-filled, multi-dose pen that delivers ***once-daily*** doses of 0.6, 1.2, 1.8, 2.4, or 3.0 mg (6.0 mg/mL, 3.0 mL) (Saxenda USPI).

On Day 1, subjects randomly assigned to open-label liraglutide will receive instruction on the use of the pre-filled multi-dose pen. Subjects will receive the first dose of study drug at the site under the supervision of study staff.

The dosage of liraglutide to be used in this study is consistent with the approved labeling for its use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients. The starting dosage of liraglutide on Day 1 will be 0.6 mg/day. At the beginning of Weeks 1, 2, 3, and 4, subjects will be contacted preferably by telephone and instructed to up-titrate their daily dose to 1.2, 1.8, 2.4, and 3.0 mg in 0.6 mg weekly increment. At Week 5, subjects will return to the clinic and should already be up-titrated to their daily dose of 3.0 mg and remain on this dose for the remainder of the treatment phase. A diagram of the titration schedule is shown in Figure 3.

Figure 3: Liraglutide Titration Schedule



For subjects who experience significant GI intolerance within the weeks prior to the Week 5 visit, up-titration of liraglutide may be delayed by 1 week; the reason for delaying up-titration will be documented on the study drug diary and eCRF. If a subject cannot tolerate the 3.0 mg

dose of liraglutide by Week 6, they should be discontinued from study treatment, as the efficacy of liraglutide for weight management has not been established at lower doses (Saxenda USPI). No dose down-titration is allowed.

Drug Administration

Injections of JNJ-64565111 (or matching placebo) and liraglutide can be done at any time of day irrespective of meals. However, it is preferable that the general time of day (ie, morning, evening, just prior to bed, etc) for injecting study drug be kept consistent, to the extent possible.

General instructions for dosing procedures and storage of study drug (or matching placebo) are provided below. Detailed instructions for dosing procedures and storage conditions of JNJ-64565111, matching placebo, and liraglutide will be provided to the study site in an additional guidance document that is provided separately.

Double-blind JNJ-64565111 or Matching Placebo

Subjects randomly assigned to double-blind JNJ-64565111 (or matching placebo) will be instructed to administer study drug SC once-weekly for the entire duration of the 26-week treatment phase or until early discontinuation. Subjects will be instructed to inject to the 4 quadrants of the anterior abdominal wall. For consistency, and to avoid dosing in the same abdominal area, subjects should be instructed to begin in one quadrant and on subsequent dosing weeks proceed in the next quadrant in a counterclockwise manner.

JNJ-64565111 (or matching placebo) should be taken on the same day of the week throughout the study (ie, the regularly scheduled study drug day). If the day of the once-weekly injection coincides with the day of a clinic visit, subjects are NOT to inject JNJ-64565111 (or matching placebo) before arriving at the clinic. Instead, AFTER all study visit procedures have been completed, subjects may self-administer blinded study drug either at the study site or once they have returned home.

Subjects are to record the date and time of study drug administration on the study drug diary. Subjects should mark a calendar to remind them of when to take the next weekly dose.

Subjects in the JNJ-64565111 (or matching placebo) groups should be instructed not to take 2 doses within 3 days (72 hours) of each other. If a subject misses taking the next dose of JNJ-64565111 (or matching placebo) on their regularly scheduled study drug day, the missed dose should be taken as soon as possible, if there are at least 3 days (72 hours) until their next regularly scheduled study drug day. If there are less than 3 days remaining, the subject should skip the missed dose and take the next dose on their regularly scheduled study drug day.

Open-label Liraglutide (Saxenda®)

Subjects randomly assigned to open-label liraglutide will be instructed to administer study drug SC once daily for the entire duration of the 26-week treatment phase or until early drug discontinuation.

Liraglutide solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

Subjects may administer liraglutide SC either in the abdomen, thigh, or upper arm. The injection site may be changed at any time. If the same injection area is being used, subjects will be instructed to choose different injection sites in that area (eg, rotating through different abdominal quadrants).

On the days of scheduled clinic visits, subjects in the open-label liraglutide group should be instructed NOT to inject liraglutide before arriving at the clinic. Instead, AFTER all study visit procedures have been completed, subjects may self-administer liraglutide either at the study site or once they have returned home.

If a dose of liraglutide is missed, the once-daily regimen should be resumed with the next scheduled dose. An extra dose should not be taken to make up for the missed dose.

- After an interruption of more than 6 days, the subject who had already reached the 3.0 mg dose level should re-initiate liraglutide with a starting dose of 1.8 mg and re-up-titrate to 3.0 mg.
- For an interruption of 4 to 6 days in duration, it will be up to investigator's judgment to assess whether the subject should re-start at 3.0 mg daily dose, or re-start at 1.8 mg or 2.4 mg.

If, after an interruption of at least 4 days, the subject re-starts at a dose of 1.8 mg or 2.4 mg. The dose should be up-titrated in 0.6 mg increment every 7 days until the full dosage of 3.0 mg is reached.

Drug Storage

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Double-blind JNJ-64565111 or Matching Placebo

Double-blind JNJ-64565111 or matching placebo supplies should be stored in the refrigerator at 36 to 46°F (2 to 8°C) and kept in their carton until ready for use and protected from direct heat and light. Blinded study drug or matching placebo can be left out at room temperature up to 8 hours. Avoid shaking blinded study drug.

Open-label Liraglutide (Saxenda®)

Prior to first use, liraglutide pens should be stored in the refrigerator at 36 to 46°F (2 to 8°C) and protected from direct heat and light. Do not store in the freezer or directly adjacent to the refrigerator cooling element. Liraglutide pens should not be frozen; if the pen is frozen, it should be thrown away.

After initial use of the liraglutide pen, it is preferably to be stored in a refrigerator (36 to 46°F; 2 to 8°C). Alternatively, it may be stored at controlled room temperature (59 to 86°F; 15 to 30°C) for up to 30 days only. The pen cap should be kept on when not in use.

To reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy, subjects should be instructed to always remove and safely discard the needle after each injection and store the liraglutide pen without an injection needle attached.

7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with blinded (based on unused safety injector(s), empty study drug carton(s), and/or study drug diary) and open-label study drug (based on unused pen, partially or fully used pen(s), empty study drug carton(s), and/or study drug diary) should receive counseling on the importance of dosing compliance.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or following study procedures.

8. PRE-STUDY AND CONCOMITANT THERAPY

Pre-study therapy includes any therapy used before the first dose of treatment phase study drug. Concomitant therapy is any therapy used after the first dose of treatment phase study drug that is administered on Day 1.

Pre-study therapies administered up to 30 days before first dose of treatment phase study drug must be recorded.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, different from the study drug must be recorded as pre-study therapy (before the first dose of treatment phase study drug) or concomitant therapy (after first dose of treatment phase study drug) on the eCRF.

Prohibited Therapies

1. Prescription weight-management drugs (including but not limited to orlistat, topiramate and/or phentermine, lorcaserin, naltrexone and/or bupropion, or over-the-counter weight-loss medications or therapies
2. Oral, intravenous, or intramuscular corticosteroids for longer than 2 consecutive weeks in duration

   Note: Inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses are allowed

3. Previous (ie, within 12 weeks from screening visit) or current use of HAART
4. Antihyperglycemic agents (including sulfonylureas, metformin, DPP-IV inhibitors, meglitinides, acarbose, thiazolidinediones, exenatide, GLP-1 or GLP-1 analogues, pramlintide, sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin, colesevelam, or bromocriptine).

   Note: Metformin is allowed in subjects who develop hyperglycemia during the double-blind treatment period
5. Antipsychotic drugs
6. Anticonvulsants, including barbiturates, GABA analogues, hydantoins, phenyltriazines, succinimides, valproic acid and its derivatives, carbamazepine, zonisamide, and felbamate
7. Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists
8. In the subset of subjects participating in the 24-hour ABPM sub-study, beta-blockers and calcium-channel blockers
9. Any other investigational agents during the study

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY PROCEDURES AND EVALUATIONS

The Time and Events Schedule summarizes the frequency and timing of scheduled visits, and the timing of efficacy, safety, PK, PRO, and other measurements applicable to this study.

9.1. General Procedures

9.1.1. Visit Schedule and Visit Windows

Screening and run-in scheduled study visits should generally occur within a 3-day window (ie, ± 4 days) and after randomization (from Day 1) scheduled study visits should generally occur within a 7-day window (ie, ± 7 days) around the protocol-specified visit schedule (as provided in the Time and Events Schedule). For study visits that cannot be held within the recommended visit window, the visit should be conducted as closely as possible to the study visit schedule. All subsequent visits should be scheduled relative to the date of randomization (Day 1), and not the date of the rescheduled visit.

9.1.2. Maximum Blood Volume Collected

The maximum blood volume (for blood collections shown in the Time and Events Schedule) that would be collected if a subject were to complete the 4-week follow-up visit after the Week 26/EOT visit would be approximately 176.0 mL for subjects randomly assigned to the blinded JNJ-64565111 or placebo treatment arms and approximately 137.5 mL for subjects randomly assigned to the open-label liraglutide treatment arm. See Table 3 below for details.

Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and/or eCRF.

Table 3: Maximum Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per subject randomized to JNJ-64565111 or matching placebo	Total Volume of Blood (mL)[a]	No. of Samples per subject randomized to liraglutide	Total Volume of Blood (mL)[a]
Hematology	2.0	3	6.0	3	6.0
HbA_{1c}	2.0	3	6.0	3	6.0
Serum chemistry	2.5	8	20.0	8	20.0
Calcitonin	2.5	4	10.0	4	10.0
Serum ß-hydroxybutyrate	2.5	6	15.0	6	15.0
Fasting insulin	2.0	2	4.0	2	4.0
Fasting C-peptide	2.0	2	4.0	2	4.0
FPG	2.0	7	14.0	7	14.0
Fasting lipid panel	3.5	4	14.0	4	14.0
Serum β-hCG pregnancy tests	2.5	2	5.0	2	5.0
FSH	2.5	1	2.5	1	2.5
Pharmacokinetic (PK) - trough and immunogenicity samples[b]	5.0	7	35.0	0	0
PK non-trough	3.5	1	3.5	0	0
Plasma, serum archive samples	18.5	2	37.0	2	37.0
Approximate Total			176.0		137.5

HbA_{1c} = hemoglobin A_{1c}; hCG = human chorionic gonadotropin; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone

[a] Calculated as number of samples multiplied by amount of blood per sample.

[b] Blood samples for PK and anti-JNJ-64565111 antibodies will only be collected from subjects randomly assigned to the double-blind JNJ-64565111 or placebo arms; these samples will not be collected from subjects randomly assigned to open-label liraglutide.

9.2. Sub-study Procedures

9.2.1. 24-hour Ambulatory Blood Pressure Monitoring [Sub-study]

The 24-hour ABPM sub-study will be performed at selected sites and in a subset of approximately 120 subjects (approximately 15 subjects each in the placebo and JNJ-64565111 5 mg groups, and 30 subjects each in the JNJ-64565111 7.4 mg, JNJ-64565111 10 mg, and liraglutide groups) who meet the specific criteria for subjects participating in the 24-hour ABPM sub-study (described in Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria). Subjects who do not meet these specific criteria (eg, due to concomitant use of beta-blocker or calcium-channel blockers) but who meet all other eligibility criteria may be enrolled in the main study and will not be required to undergo the ABPM procedure.

Eligible subjects will return to the study site prior to the Day 1 visit (on Day -2 or Day -1) and will be dispensed an ABPM device in an appropriate size. The device will be set up by study staff and placed on the non-dominant arm to obtain the 24-hour ABPM baseline measurement; the ABPM readings will be masked. Study staff will turn on the device and instruct the subjects on how to wear the device. Subjects will be given the ABPM diary and instructed to record events such as chest pain, chest discomfort, palpitations, tachycardia dizziness, lightheadedness, hypotension, orthostatic hypotension, near syncope, syncope, etc. Subjects will be instructed to record time and date of such events, concomitant activities (eg, physical exercise), and if

possible obtain an additional reading of blood pressure using the ABPM device. This diary will be reviewed by study-site personnel at each scheduled visit. Subject-reported events considered by the investigator to be AEs will also be recorded on the AE eCRF.

After 24 hours, subjects will return to the study site and the device will be removed from the subject, the data will be transferred, and an assessment will be made of whether or not the readings are valid using the definition of 'valid' in the ABPM inclusion criterion (ie, at least 22 hours of recording with ≥70% of valid scheduled readings, and no continuous interruption of >2 hours of recording).

Subjects who have valid baseline ABPM readings and who meet all other enrollment criteria may be randomized on Day 1. If the subject does not have a valid baseline ABPM reading due to technical issues (eg, breakage of device components) or the subject has unexpected illness or other circumstance during the day(s) of the 24-hour ABPM recording that could confound the assessment of the endpoint, at the discretion of the investigator, the subject may repeat the procedure within 1 week prior to randomizing subject to first study dose. If the 24-hour repeat recording is successful, this repeat recording will be used as the subject's baseline 24-hour ABPM. If no valid ABPM reading is obtained following the second attempt, the subject should be excluded from the ABPM sub-study, but may be randomized into the main study if they continue to meet other eligibility criteria. In this case, the subject should not undergo the ABPM procedure at the Week 26/EOT visit.

Subjects will repeat the procedure 1 or 2 days prior to the Week 26/EOT visit in subjects who have not withdrawn consent from the study, died, or were lost to follow-up. For subjects treated with JNJ-64565111 or matching placebo, every effort should be made to have the procedure performed within 7 days from the previous dose of study drug. Subjects treated with open-label liraglutide should continue to their daily dosing schedule. If the subject does not have a valid Pre-Week 26 ABPM reading due to technical issues (eg, breakage of device components) or the subject has unexpected illness or other circumstance during the day(s) of the 24-hour ABPM recording, at the discretion of the investigator, the site may delay subject's Week 26/EOT visit up to another week, and the subject will be asked to repeat the procedure within 1 week prior to coming to Week 26/EOT visit. If needed, additional study drug may be dispensed to allow dosing 7 days prior to the repeat ABPM procedure. If the 24-hour repeat recording is successful, this repeat recording will be used as the subject's Week 26/EOT ABPM.

9.3. Pre-treatment Phase Procedures and Evaluations

9.3.1. Screening Visit (Week -3)

Potential subjects will have all screening procedures as noted in the Time and Events Schedule completed within 1 week (Week -3). Eligible subjects must meet all of the eligibility criteria (see Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria).

Informed Consent must be signed at the screening visit before any study procedures are performed. If participating sites do not have a written policy that subjects typically are invited to the site in a fasting condition, an optional pre-screening visit will be necessary to obtain written informed consent prior to inviting subjects in a fasting state for the screening procedures.

9.3.2. Run-in Phase (Week -2 to Day -1)

At the Week -2 run-in visit, subjects will complete a baseline assessment for IWQOL-Lite, single item Ease of Weight Management, and the PAM; subjects should complete the PRO measures (whenever possible) before any training, tests, procedures (including ECG and injection-training), discussion of AEs or the subject's medical condition, or other consultations to prevent influencing subject's perceptions (see Attachment 9, Instructions for the Completion of PRO Assessments). In cases where a final translated version of the assessment does not exist in the language spoken by the subject, the assessment should not be administered. English-speaking subjects in selected countries only will also complete the PROMIS SF 8b, PGIS, and be provided a PRO diary for them to complete the ERCQ at home. The ERCQ should be completed by the subject each day at the same time each day, in the same setting each day, for the 7 consecutive days immediately prior to the Randomization visit (eg, starting 7 days before the randomization visit).

An assessment of eligibility criteria will be completed (see Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria) and pre-study drugs will be reviewed. The investigator or designated study-site personnel will perform a 12-lead local ECG.

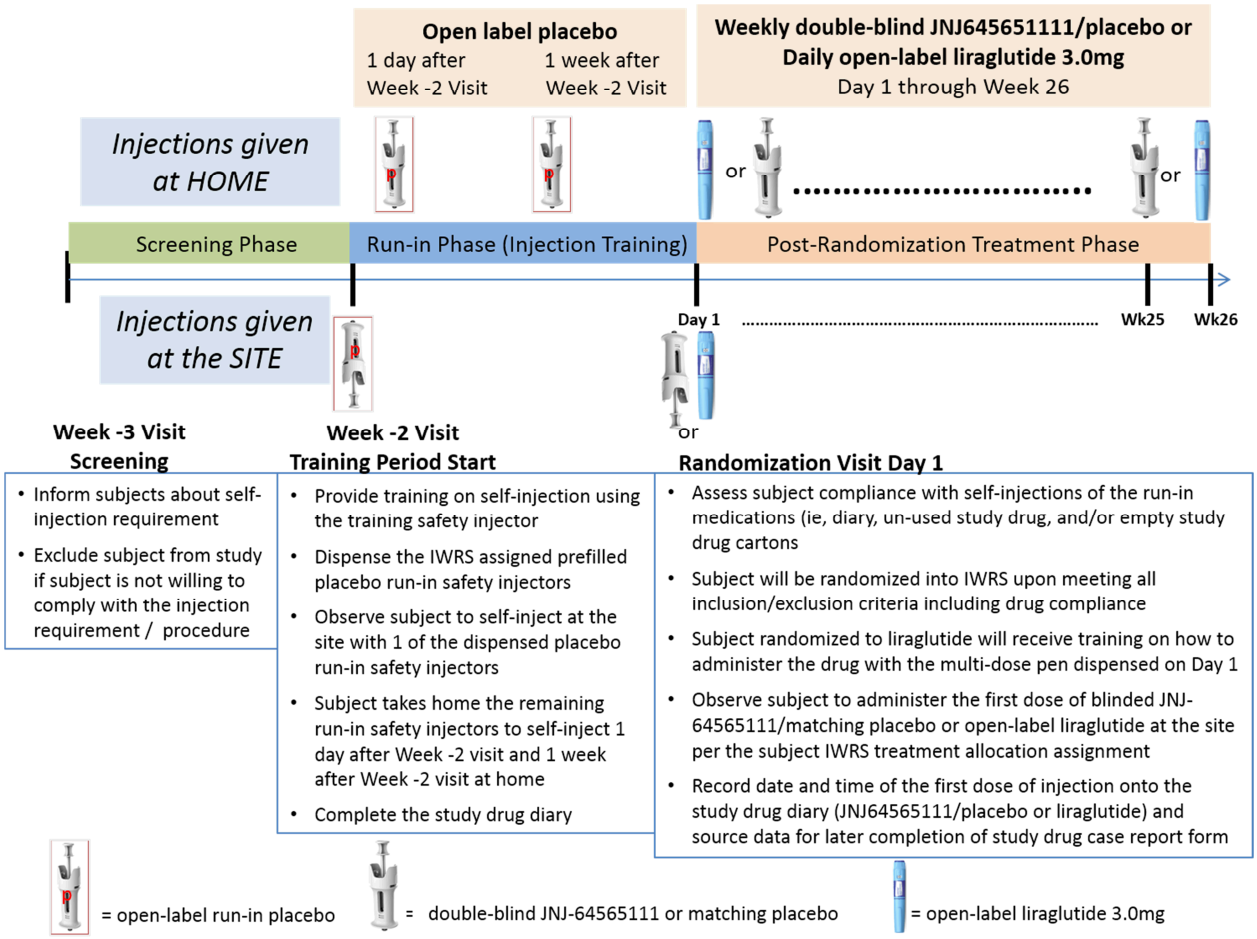
Details on specific procedures performed during this phase are described below.

9.3.2.1. Training on Subcutaneous Drug Administration

At the Week -2 visit, subjects will receive pre-filled safety injectors containing 0.5 mL of placebo. Subjects will be informed that they are receiving placebo during the run-in phase and that the purpose of these injections is to train them on the injection technique and to assess compliance with dosing regimen. The investigator or designated site personnel will instruct each subject on how to perform self-injections. Each subject will use a pre-filled safety injector to perform a self-injection under the supervision of the study staff. If, after the training, the subject is still willing to participate in the study and perform weekly self-injections, the subject will be given a supply of placebo pre-filled safety injectors to take home, and instructed to administer injections of open-label placebo weekly at home. Subjects will also receive a study drug diary, and will be instructed to record the date and time of each SC self-injection.

A diagram of the injection-training procedures is provided in Figure 4.

Figure 4: Injection-training Procedures



9.3.2.2. Study Drug Diaries

Subjects will receive the study drug diary and be instructed to record the date and time of each self-injection throughout the run-in and treatment phase which allows an assessment of treatment compliance and the relationship of PK measurements and safety assessments in relation to dosing of study drug. The information will be entered into eCRFs by the site personnel.

9.3.2.3. Pre-day 1 Visit (ABPM Sub-study Subjects Only)

Subjects participating in the 24-hour ABPM sub-study will return to the study site 1 or 2 days prior to Day 1 to receive the ABPM device and diary and obtain a 24-hour ABPM baseline measurement (see Section 9.2.1, 24-Hour Ambulatory Blood Pressure Monitoring [Sub-study]).

9.4. Treatment Phase Procedures and Evaluations

Please refer to the Time and Events Schedule for the visit schedule and study procedures during the treatment phase.

9.4.1. Day 1/ Day of Randomization

At baseline (Day 1), subjects will return any unused placebo pre-filled safety injector(s), empty study drug carton(s), and/or subject study drug diary to the study site. Study-site staff will count the unused placebo pre-filled safety injectors, empty study drug carton(s), and/or the number of injections recorded on the subject study drug diary to assess compliance.

Subjects who continue to express willingness to self-administer SC injections, and continue to meet all study entry criteria, including compliance with the open-label placebo run-in medication (see Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria) will be randomly assigned to a treatment group using the IWRS (as described in Section 5, Treatment Allocation and Blinding).

English-speaking subjects in selected countries only will complete the PROMIS SF 8b and participate in an ACTT interview. All subjects should complete the PRO measure (whenever possible) before any training, tests, procedures, discussion of AEs or the subject's medical condition, or other consultations to prevent influencing subject's perceptions (see Attachment 9, Instructions for the Completion of PRO Assessments). The Run-in Phase ERCQ PRO diary should be collected from the subset of subjects for whom it was distributed, and it should be checked for completeness. For subjects who participate in the 24-hour ABPM sub-study during the run-in phase, data will be transferred from the ABPM device and an assessment will be made (see Section 9.2.1).

Counseling should be done by dietitians/nutritionists on Day 1/Day of Randomization to provide an assessment and recommendation for a reduced-calorie diet and exercise regimen (see Attachment 4). At subsequent visits (Weeks 5, 10, 15, and 20), counseling and reinforcement of the recommended diet and exercise regimen may be conducted by a trained counselor. Subjects will be instructed to not start any other diet or new exercise program during the study.

Anthropometric measurements, for body weight, height, and waist circumference measurement procedures, are described in Attachment 3.

Subjects randomly assigned to the JNJ-64565111 or placebo treatment groups will be dispensed a 6-week supply of blinded study drug according to their treatment group assignment. The first dose of blinded study drug will be self-administered at the study site in the presence of study staff after all baseline procedures have been completed. Subjects will be instructed to administer study drug or matching placebo SC once-weekly at home (as described in Section 6.2, Post-Randomization Double-blind JNJ-64565111 or Matching Placebo and Open-label Liraglutide).

For subjects randomly assigned to the open-label liraglutide treatment group, study staff will train the subjects on the use of the dial-a-dose auto-injector pen. The first dose of open-label liraglutide will be self-administered at the study site in the presence of study staff after all baseline procedures have been completed. Subjects will be instructed to administer open-label liraglutide SC once daily at home.

9.4.2. Weeks 1, 3, 4, and 24 Contact

Subjects in the open-label liraglutide treatment group will be contacted preferably by telephone at Weeks 1, 3, and 4 to remind them about their dosing titration (ie, to increase their dose of liraglutide by an 0.6 mg dose increment weekly) (see Section 6.2, Post-Randomization Double-blind JNJ-64565111 or Matching Placebo and Open-label Liraglutide).

Only English-speaking subjects participating with ERCQ will be contacted preferably by telephone at Week 24 to remind about the ERCQ diary completion.

9.4.3. Weeks 2, 5, 10, 15, 20 Visits

Please refer to the Time and Events Schedule for the study procedures at each visit. In between Weeks 2, 5, 10, 15, and 20 visits, site staff is encouraged to contact subjects to reinforce the adherence to diet and exercise, study drug dosing reminder, assessment of subjects' status, and compliance with the protocol procedures (eg, diary completion reminder).

9.4.4. Pre-Week 26 Visit (ABPM Sub-study Subjects Only)

Those subjects participating in the 24-hour ABPM sub-study will return to the study site at 1 or 2 days prior to the Week 26/ EOT visit to repeat the ABPM procedure. For subjects treated with JNJ-64565111 or matching placebo, every effort should be made to have the procedure performed within 7 days from the previous dose of study drug.

If the subject does not have a valid Pre-Week 26 ABPM reading due to technical issues (eg, breakage of device components) or the subject has unexpected illness or other circumstance during the day(s) of the 24-hour ABPM recording, at the discretion of the investigator, the site may delay subject's Week 26/EOT visit to another week and the subject will be asked to repeat the procedure within 1 week prior to coming to Week 26/EOT visit. If needed, additional study drug may be dispensed to allow dosing 7 days prior to the repeat ABPM procedure. If the 24-hour repeat recording is successful, this repeat recording will be used as the subject's Week 26/EOT ABPM.

9.4.5. End-of-Treatment/Early Study Drug Discontinuation

See the Time and Events Schedule for procedures to be conducted at the EOT evaluation.

The EOT evaluations will be performed when the subject completes the 26-week treatment phase or prematurely discontinues study drug prior to Week 26. Every effort should be made to have the Week 26/ EOT visit scheduled within 7 days after the last dose of study drug.

Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of early study drug discontinuation or as soon as possible following study drug discontinuation).

Site-based PRO instruments will be completed during the Week 26/EOT visit (ie, IWQOL-Lite, Ease of Weight Management, PAM, PROMIS SF 8b, PGIS, and PGIC). The final ERCQ diary will be collected by the site and reviewed for completeness at Week 26. For subjects who

discontinue early from study drug prior to Week 26, no ERCQ diary completion is required at the EOT visit. English-speaking subjects in selected countries only will be given a STEP Interview (see Section 9.7.3, Patient-reported Outcomes).

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

9.4.6. Management of Hyperglycemia

Throughout the 26-week treatment phase, subjects who develop hyperglycemia and have FPG values of ≥140 mg/dL (7.8 mmol/L) should receive reinforcement of diet and exercise recommendations followed by an FPG repeat within 14 days by the central laboratory. If the FPG repeat value is still ≥140 mg/dL (7.8 mmol/L), subjects will initiate metformin therapy at an initial dose and with dose titration managed by the investigator as considered clinically appropriate and consistent with local prescribing information. Male subjects with a serum creatinine ≥1.5 mg/dL (133 µmol/L), or female subjects with a serum creatinine ≥1.4 mg/dL (124 µmol/L), or subjects who have any other contraindication to metformin use (including eGFR per local prescribing information of the country of the investigational site), are not eligible for metformin therapy and should have their study drug discontinued and undergo an early withdrawal visit.

Investigators must complete the appropriate eCRF page (documenting initiation of therapy) for subjects starting metformin medication.

Double-blind study drug and open-label liraglutide must be continued after initiation of metformin therapy.

Once subjects have initiated metformin, they should be counseled to monitor their fasting self-monitored blood glucose (SMBG) at least 2 times a week (or more frequently if deemed necessary by the investigators) throughout the duration of the study and to contact the site if fasting SMBG values are consistently >180 mg/dL (10.0 mmol/L).

Subjects on metformin therapy for at least 2 weeks at the maximum tolerated dose of metformin (or maximum dose considered appropriate by the investigator) with FPG >180 mg/dL (10.0 mmol/L), must be discontinued from the study (see Section 10.2, Discontinuation of Study Treatment)

9.5. Post-treatment (Follow-up) Procedures and Evaluations

Subjects who complete the 26-week treatment phase will be asked to return for the 4-week SAE follow-up visit approximately 5 weeks after the last dose of study drug for JNJ-64565111-treated or placebo-treated subjects and 4 weeks after the last dose of study drug for liraglutide-treated subjects to collect any SAEs unless the subject has died, is lost to follow-up, or has withdrawn consent. If the subject has died, the date and cause of death will be collected and documented. For subjects randomly assigned to double-blind JNJ-64565111 or placebo only, blood samples

will be collected at the 4-week SAE follow-up visit for PK and immunogenicity (ie, ADA) measurement. In addition, during this visit, subjects who received metformin therapy, regardless of whether randomly assigned to double-blind JNJ-64565111 or open-label liraglutide, will also have blood sample collected to measure FPG.

In addition, subjects who prematurely discontinue study drug for any reason prior to Week 26 and have not withdrawn consent, were not lost to follow-up, or did not die, will continue in the study following the EOT visit to undergo the following off-treatment procedures based on the predefined visit schedule outlined in the Time and Event schedule.

These will include collection of:

- SAEs
- Specific AEs of interest (ie. MACE events, acute pancreatitis, and possible cases of thyroid neoplasm)
- Vital signs (including body weight)
- Concomitant medications

NOTE: If the 4-week SAE follow-up visit is expected to occur within 2 or 3 weeks from the next scheduled off-treatment visit, the site may combine both visits and perform all procedures of the combined visits. For example, assuming a subject discontinued study drug at Week 5 (EOT visit) and therefore 4-week SAE follow-up visit is expected to occur at Week 9, this visit can be combined with the off-treatment scheduled Week 10 visit. These 2 visits can be combined to perform the assessments/procedures from both visits as indicated on the Time and Event schedule (no duplicate procedures are required if they are scheduled at both visits).

If subjects that discontinued study drug early are unable to return to their site for the scheduled on-site study visit, an alternate contact visit should be conducted with the goal of collecting any SAEs, MACE events (ie, CV death, nonfatal MI and nonfatal stroke), AEs of thyroid neoplasm and pertinent concomitant medications. Details regarding discussions via telephone, email, or other methods of contact must be properly documented on subject's source record and/or applicable eCRFs, such as date of contact, outcome and/or responses provided by the subjects. The site may consult subjects' delegated contact(s) for the off-treatment follow-up if the site is unable to reach the subjects after multiple attempts.

9.6. Internal Data Monitoring Committee (DMC)

An iDMC will be established to monitor safety data on an ongoing basis. The committee will meet periodically to review interim data. After the review, the iDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate iDMC charter.

The iDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The iDMC responsibilities, authorities, and procedures will be documented in its charter.

In addition to iDMC unblinded monitoring, the study team will perform ongoing blinded monitoring and will alert the iDMC to any possible safety signal the blinded team notes during their review of the data.

9.7. Efficacy Evaluations

9.7.1. Primary Efficacy Endpoint

The primary measure of efficacy is percent change in body weight. The primary efficacy endpoint will be the percentage change in body weight from baseline to Week 26 between JNJ-64565111 compared to placebo.

9.7.2. Secondary and Exploratory Efficacy Endpoints

The secondary measures of efficacy at Week 26 include proportion of subjects with ≥5% and ≥10% weight loss from baseline, and absolute change in body weight from baseline.

Exploratory efficacy endpoints at Week 26 include change from baseline in BMI, waist circumference, fasting lipids (total cholesterol, LDL-C, HDL-C, and triglycerides), FPG, fasting insulin, fasting C-peptide, serum ß-hydroxybutyrate, SBP, DBP, pulse rate, PK exposure, and PROs (ie, changes in IWQOL-Lite, single item Ease of Weight Management, PAM, ERCQ [subset of subjects], and PROMIS SF 8b [subset of subjects]).

Additional exploratory endpoints assessed in a subset of subjects at Week 26 include qualitative assessments of pre-trial expectations and post-trial experiences using the ACTT pre-trial interviews and a modified STEP exit interview in English-speaking subjects in selected countries only.

The effects of JNJ-64565111 compared with liraglutide on the percentage change and absolute change in body weight from baseline and the proportion of subjects with ≥5% and ≥10% weight loss from baseline will also be assessed at Week 26.

9.7.3. Patient-reported Outcomes

Janssen is developing a novel PRO instrument (ie, ERCQ) to assess eating-related concepts such as hunger, appetite, cravings and/or satiety, and to support the use of an existing PRO instrument assessing physical functioning. These novel measures along with previously developed questionnaires will be included in this study. Some questionnaires will be completed during scheduled site visits while others will be completed at home by the subject. It is therefore important for sites to be familiar with the PRO Time & Events schedule to ensure subjects complete the PROs at the correct setting and visit. These PROs will enable the evaluation of subject's experience of treatment and although the PRO endpoints are exploratory, the expected treatment-group differences may provide data supporting the value of the product from a patient's perspective.

All site visit-based PRO assessments (whenever possible) should be completed before any tests, procedures, or discussion of AEs or the subject's medical condition (see Attachment 9, Instructions for the Completion of PRO Assessments). The home-based PRO assessments (ERCQ) should be completed daily at the same time whenever possible and in the same setting for 7 consecutive days immediately prior to the next visit.

The Impact of Weight on Quality of Life-Lite (IWQOL-Lite)

The IWQOL-Lite (Kolotkin 2001; Kolotkin 2002) is a 31-item, self-report obesity-specific measure that contains 5 domains: Physical Function (11 items), Self-esteem (7 items), Sexual Life (4 items), Public Distress (5 items), and Work (4 items). It has been used to quantitatively assess an individual's perception of how their weight affects their day-to-day life. The IWQOL-Lite has been widely used in clinical trials and is a reliable and valid measure that has demonstrated good psychometric properties.

Confirmatory factor analyses provide strong support for the adequacy of the scale structure. The 5 identified scales and the total score demonstrated excellent psychometric properties in obese patients (Coon 2016; Hauber 2010), and the reliability of the scales ranges from 0.90 to 0.94 and is 0.96 for the total score (Kolotkin 2001). A published algorithm is used to calculate domain and total scores, which range from 0 to 100 with higher scores indicating better well-being. IWQOL-Lite will be administered at Weeks -1, 15, and 26/EOT. A sample of the IWQOL-Lite that contains representative questions and instructions for completion are provided in the PRO Completion Guidelines.

IWQOL-Lite will be completed at Week -2, 15, and 26/EOT visits.

Single Item Ease of Weight Management

A single item developed by the sponsor that inquires, "How difficult is it for you to lose weight?" will be completed at Weeks -2, 15, and 26/EOT visits. A sample of the single item assessing Ease of Weight Management is provided in the PRO Completion Guidelines.

Patient Activation Measure (PAM)

A 13-item self-report measure that identifies where individuals place within 4 different levels of activation. It reliably predicts future emergency room visits, hospital admissions and readmissions, and medication adherence (Hibbard 2005).

PAM will be completed during the Week -2, 15, and 26/EOT visits.

Eating-related Concepts Questionnaire (ERCQ)

An instrument developed by the sponsor describes the subject's rating eating-related concepts such as hunger, appetite, cravings, and satiety. The ERCQ follows the FDAs Guidance for Industry for developing new PRO measures (FDA 2009).

At Week -2 visit, English-speaking subjects in selected countries will be provided the ERCQ diary to complete at home. The ERCQ should be completed by the subject at the same time and in the same setting each day for 7 consecutive days, starting at Week -1 up to the day prior to Day 1 visit.

At Week 15 visit, subjects who completed ERCQ diary for 7 consecutive days prior to Day 1 visit will be provided a new diary to complete at home. The ERCQ should be completed by the subjects at the same time and in the same setting each day for the following 7 consecutive days after the Week 15 visit. The completed ERCQ diary should be returned to the site at the Week 20 visit and another ERCQ diary will be provided to the subjects at that visit. The site should contact subjects at Week 24 preferably by telephone to remind the completion of this ERCQ diary. Subjects should begin completing this ERCQ diary for 7 consecutive days starting at Week 25 up to the day prior to their scheduled Week 26 visit. The completed final ERCQ diary should be returned by the subjects and collected by the site at the Week 26 visit. For subjects who discontinue early from study drug, no ERCQ diary completion is required at the EOT visit.

PROMIS Physical Function Short Form 8b

PROMIS® (Patient-Reported Outcomes Measurement Information System) is a set of person-centered measures that evaluate physical, mental, and social health in adults and children (HealthMeasures website). These measures can be used with the general population and with individuals living with chronic conditions. PROMIS Profile instruments are a collection of short forms containing a fixed number of items from different domains (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities). The PROMIS Profile instruments are administered as short forms and are ideal when researchers prefer to ask the same question of all respondents or of the same respondent over time. These measures were developed and validated with state-of-the-science methods to be psychometrically sound (HealthMeasures website).

In English-speaking subjects in selected countries only, PROMIS SF 8b will be administered at Week -2, Day 1, Week 15, and Week 26/EOT visits.

Patient Global Impression Status (PGIS) and Patient Global Impression of Change (PGIC)

Interpreting meaningful change in scores on PRO instruments is an important step in instrument development. The methods for interpreting meaningful change to derive responder definitions have evolved over time and various approaches exist. Yet, in many cases, anchor-based methods are preferred over distribution-based methods. Anchor-based methods link scores on the PRO to an external criterion that identifies subjects who have experienced an important change in their condition. Distribution-based approaches use the variability of PRO scores to quantify the magnitude of change (Coon 2016). The PGIS and the PGIC will be used as anchors, external criterion, to determine meaningful change in scores for the ERCQ and the PROMIS SF 8b in this population of non-diabetic severely obese subjects. The PGIS contains questions on how the subject would currently rate their ability on the concept(s) of interest. The PGIC contains questions on how the subject would rate their ability on the concept(s) of interest compared to before starting the study.

In English-speaking subjects in selected countries only, PGIS will be administered at Week -2, Week 15, and Week 26/EOT visits, and PGIC at Week 15 and Week 26/EOT visit only.

9.7.4. Interviews

In English-speaking subjects in selected countries only, study entry (ACTT) and exit (STEP) structured qualitative interviews will be conducted to qualitatively describe pre-treatment goals and expectations and post-treatment experiences.

At Day 1 visit, English-speaking subjects in selected countries will be given an ACTT interview. At Week 26/EOT visit, the English-speaking subjects in selected countries will be given a STEP Interview.

The principal investigator should use their discretion to determine whether the subject is sufficiently fluent in English to take the ACTT and STEP surveys.

Pre- and post-treatment interviews have been used in early phase clinical trials to inform exploratory insight into patient experiences of new medications. The data from these interviews will not be reconciled with the safety database of the study. These interviews are semi-structured and are designed to allow subjects to provide their own impressions of a study drug and not be restricted to items included in standard questionnaires.

9.8. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK of JNJ-64565111, as well as immunogenicity based on measurement of anti-JNJ-64565111 antibodies. Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.8.1. Pharmacokinetic Evaluations

9.8.1.1. Sample Collection and Handling

Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Blood collections for PK assessments should be kept as close to the specified time as possible.

In all subjects randomly assigned to JNJ-64565111 or matching placebo (but not in subjects randomly assigned to open-label liraglutide), venous blood samples will be collected according to the Time and Events Schedule for determination of serum trough concentrations of JNJ-64565111 to assess attainment of steady-state concentrations. In addition, a post-treatment sample at 30 weeks will also be collected in all subjects. On the days of the trough clinic visits at which PK samples are to be obtained, subjects are not to inject the study drug before arriving at the clinic.

The PK sampling scheme was prospectively optimized for population-based PK analyses. In addition to the trough samples and a post-treatment sample in all subjects, a subset of subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample.

The non-trough PK visit will occur at selected sites and will involve approximately 180 subjects (approximately 45 subjects each in the placebo, JNJ-64565111 5 mg, JNJ-64565111 7.4 mg, JNJ-64565111 10 mg groups). A sample size of 45 subjects per dose group was based on (1) optimal PK sampling based on Fisher Information Matrix to allow precise estimation of population PK parameters and (2) logistical constraints to limit the number of additional patient visits for PK sampling.

The exact dates and times of previous study drug injection and blood sampling for PK must be recorded in the eCRF or laboratory requisition form for all PK samples.

See the laboratory manual for information regarding handling of biologic samples.

9.8.1.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of JNJ-64565111 using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

9.8.1.3. Pharmacokinetic Parameters

Serum concentrations at each time point of measurement will be evaluated by descriptive statistics. In addition, to develop a structural PK model of JNJ-64565111 and to evaluate the dependence of the pharmacokinetics of JNJ-64565111 on population covariates, all PK data from subjects in this study will be combined with data from other clinical studies of JNJ-64565111 for a pooled population PK analysis. This will be performed using nonlinear mixed-effects modeling with the software package NONMEM©. The mean (and variance) values for specific PK parameters (eg, clearance) will be estimated and the statistical significance of the relationships between covariates and PK parameters will be evaluated. This pooled analysis will be reported separately.

9.8.2. Immunogenicity Assessments (Anti-JNJ-64565111 Antibodies)

The detection and characterization of anti-JNJ-64565111 antibodies will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of anti-JNJ-64565111 antibodies will also be evaluated for JNJ-64565111 serum concentration to enable interpretation of the antibody data.

Anti-JNJ-64565111 antibodies will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule. Additionally, serum samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study.

At visits where serum concentration of study drug and antibodies to study drug will be evaluated, one venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 3 aliquots (1 each for serum concentration of study drug, antibodies to study drug, and a back-up).

Serum samples will be screened for antibodies binding to JNJ-64565111 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to JNJ-64565111 and/or further characterize the immunogenicity of JNJ-64565111.

9.9. Archive Samples for Exploratory Research

Fasting plasma, serum, and urine samples will be collected at the time points specified in the Time and Events Schedule and archived for future exploratory research. The blood will be processed to yield plasma, which will be stored at or below -70º C. Short-term storage of samples for no more than 2 weeks at –20º C freezer is acceptable if the site does not have a freezer at –70º C or colder. Preferably, the frozen samples should be shipped to the central lab as soon as possible. Refer to the laboratory manual for detailed instructions for sample collection, processing and shipment of archive samples for exploratory research.

9.10. Safety Evaluations

Safety evaluations will include the monitoring of AEs (including protocol-specified AEs of interest), vital sign measurements, clinical laboratory tests (including calcitonin, lipase, amylase, and sodium), and serum pregnancy testing.

Investigators will remind subjects to contact the investigational sites in the presence of signs/symptoms that may be consistent with acute pancreatitis (see Attachment 6), or in the presence of severe nausea/vomiting that limits the ability of the subject to keep adequate fluid intake even for a few hours, hence increasing the risk of dehydration and electrolyte imbalances. Based on the assessment, the investigators should use their clinical judgment to determine whether the subject may require immediate medical attention (eg, emergency room visit) or whether the subjects should be scheduled as soon as possible for an unscheduled visit to undergo clinical and pertinent laboratory assessments, and if deemed appropriate by the investigator, study drug should be interrupted until results have been reviewed.

If a subject experiences an adverse event of vomiting assessed by the investigator as “severe” in intensity (see Section 12.1.3, Severity Criteria) lasting more than 24 hours and considered to be at least possibly related to study drug, the subject must be discontinued from study treatment (see Section 10.2, Discontinuation of Study Treatment).

If a subject experiences an adverse event of vomiting assessed as “moderate” in intensity lasting more than 48 hours, considered to be at least possibly related to study drug, and occurring within 3 days of the next scheduled dose, further administration of study drug will be interrupted. Based upon the investigator’s assessment of the subject’s clinical status (which may be done via a telephone contact or in-clinic visit) and/or, if necessary, a review of the laboratory results (either obtained by central or local laboratory), the investigator will determine whether the subject can resume study drug (eg, no signs/symptoms of dehydration, reduction in intensity or resolution of adverse event, no clinically significant laboratory abnormalities), should continue to interrupt study drug, or be permanently discontinued from study drug (see Section 10.2, Discontinuation of Study Treatment).

At the investigator's discretion, an anti-emetic may be administered or prescribed if needed to reduce vomiting so as to avoid subsequent dehydration.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end-of-treatment will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

Routine safety monitoring will be conducted by the internal sponsor clinical study team and will be based on the review of blinded data on a regular basis.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Collection of Protocol-Specified Adverse Events of Interest

For any adverse event considered to be one of the following protocol-specified AEs of interest, and for all deaths, investigators may be asked to provide more detailed information on supplemental form or eCRF.

Cardiovascular Events

Investigators will be instructed to identify the following cardiovascular events of interest:

- MACE (ie, CV death, nonfatal MI and nonfatal stroke)
- hypotension-related AEs

Pancreatic Events

Investigators will be instructed to identify the following pancreatic events of interest:

- AEs of pancreatitis
- AEs of serious or severe abdominal pain leading to suspicion of pancreatitis
- confirmed lipase or amylase elevations ≥3× ULN.

See Attachment 7, Pancreatitis Monitoring and Withdrawal Criteria, for details of how to monitor and document pancreatic AEs.

Calcitonin Elevation and Thyroid Neoplasm

Investigators will be instructed to identify elevations in calcitonin and possible cases of thyroid hyperplasia, including but not limited to:

- C-cell thyroid hyperplasia

- Medullary thyroid cancer
- Thyroid cancer (papillary, follicular)
- Thyroid nodule

See Attachment 8, Guidelines for Calcitonin Monitoring, for details of how to monitor and document thyroid neoplasm.

Clinical Laboratory Tests

Subjects will be monitored for safety laboratory analytes (hematology, chemistry, and urinalysis) as described in Attachment 5, Clinical Laboratory Tests.

Subjects with elevations in ALT (≥3-times ULN), in lipase/amylase (≥2 times ULN) or in calcitonin (≥10 pg/mL [≥10 ng/L]) will be monitored and managed using the algorithms provided in Attachment 6, Algorithm for Monitoring Abnormal Liver Function Tests, Attachment 7, Pancreatitis Monitoring and Withdrawal Criteria, and Attachment 8, Guidelines for Calcitonin Monitoring.

Alerts will be provided to investigators by the central laboratory identifying important laboratory changes or key out-of-range values, so the investigator can follow-up as necessary. For creatinine phosphokinase (CPK) elevations, the investigator should determine if follow-up evaluation is clinically appropriate to exclude a potential cardiac event.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF.

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Resting Vital Signs (Pulse, Blood Pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before blood sample collection for laboratory tests. Blood pressure will be assessed manually with a mercury sphygmomanometer or an automated blood pressure monitor. Three consecutive blood pressure and pulse rate readings will be taken and recorded, at intervals of at least 1 minute apart, as specified in the Time and Events Schedule and in Attachment 2, Method of Blood Pressure and Pulse Rate Measurement.

At the screening visit, blood pressure will be measured in both arms. If there is a difference between arms of >10 mm Hg in either systolic or diastolic pressure, the arm with the higher

pressure should be used to measure blood pressure and should be used for all subsequent blood pressure measurements during the study. If possible, if blood pressure is measured manually, it should be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Physical Examination

Physical examinations will include a full review of body systems (vital signs, as above, head and neck, eyes, chest and lungs, breast, CV, extremities and back, abdomen, foot, and neurologic examination). Physical examination abnormalities will be collected if considered an adverse event by the investigator (recorded on adverse event eCRF).

Electrocardiogram (ECG)

A standard 12-lead ECG will be conducted at the Week -2 visit. Electrocardiograms will be conducted and read at the investigator site or affiliated facility. Significant findings that are present must be documented in the source and eCRF.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Pregnancy Testing

Serum pregnancy testing will be conducted at screening and at the Week 26/EOT visit for all women of childbearing potential (ie, unless they are permanently sterilized or unless there is a documented history of their postmenopausal status, as defined in Section 4.1, Inclusion Criteria). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at any time during the study. Study drug should be immediately interrupted based upon a positive urine pregnancy test, and permanently discontinued if confirmed by a serum pregnancy test.

9.11. Survey on Experience with Self-injection of Study Drug

A survey designed to assess subject satisfaction with the experience of self-administering JNJ-64565111 or matching placebo or liraglutide will be given to a subset of English-speaking subjects in selected countries at Week 5. The PI should use their discretion to determine whether the subject is sufficiently fluent in English to take the survey.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ DISCONTINUATION FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments through Week 26 of the treatment phase.

The EOT evaluation should be followed by a SAE follow-up visit approximately 5 weeks after the last dose of JNJ-64565111-treated or placebo-treated subjects and 4 weeks after the last dose of study drug for liraglutide-treated subjects, as described in Section 9.5, Post-treatment Phase (Follow-Up) Procedures and Evaluations.

10.2. Discontinuation of Study Treatment/ Discontinuation from the Study

Discontinuation of Study Treatment

A subject's study treatment must be discontinued if:

- Subject's eGFR is <45 mL/min/1.73 m^2 (provided by the central laboratory)

  Note: For subjects meeting the eGFR discontinuation criterion, a repeat determination should be performed within 1 week and study treatment discontinued if the repeat determination confirms that the value still meets the criterion.

- Subject has a serum sodium of <125 mEq/L (<125 mmol/L), confirmed by repeat central laboratory measurement.

  Note: For subjects meeting the sodium discontinuation criterion, a repeat determination of the full chemistry panel should be performed within 1 week and study treatment discontinued if the repeat determination confirms that the sodium value still meets the criterion (unless a reversible acute cause is identified [eg, severe vomiting, dehydration] in which case an additional repeat determination can be performed after resolution of the illness). If the sodium value is improving on repeat determination, but value is still <130 mEq/L (<130 mmol/L), an additional repeat measurement should be performed within 1 to 2 weeks to monitor subject's electrolytes.

- Subject experiences an episode of vomiting assessed as "severe" lasting more than 24 hours and considered to be at least possibly related to study drug without any other potential cause (eg, viral gastroenteritis, food-borne illness).
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
- Subject has episodes of tachyarrhythmia (eg, atrial flutter, atrial fibrillation, ventricular tachycardia) or develops persistent resting pulse rate >100 bpm for which in the opinion of the investigator it is in the best interest of the subject to discontinue study treatment
- Liver function test abnormalities occur that meet the criteria for permanent discontinuation of study drug as outlined in Attachment 6, Algorithm for Monitoring Abnormal Liver Function Tests
- Acute pancreatitis, defined by the presence of at least 2 of the following 3 circumstances: characteristic abdominal pain, amylase and/or lipase >3X ULN or characteristic findings on CT/ MRI (see Attachment 7, Pancreatitis Monitoring and Withdrawal Criteria)
- Serum calcitonin value ≥50 pg/mL (≥50 ng/L) after baseline, a repeat determination should be performed within 2 weeks and study treatment discontinued if the repeat determination confirms that the value still meets the criterion

- The subject becomes pregnant (study drug should be immediately interrupted based upon a positive urinary human chorionic gonadotropin (hCG), and permanently discontinued if confirmed by a serum β-hCG)
- Subject requiring metformin is not eligible to initiate treatment with metformin based upon any 1 of the following criteria:
  - is a male subject with a serum creatinine ≥1.5 mg/dL (133 μmol/L), or a female subject with a serum creatinine ≥1.4 mg/dL (124 μmol/L), or
  - has any contraindication to the use of metformin (including eGFR; per local prescribing information of the country of the investigational site)
- Subject is on metformin, and after at least 2 weeks on the maximum tolerated dose (or maximum dose considered appropriate by the investigator) FPG is >180 mg/dL (10.0 mmol/L).
- Initiation and planned continued use of prohibited therapy (see Section 8, Pre-study and Concomitant Therapy).
- For liraglutide subject who cannot tolerate the 3.0 mg dose of liraglutide by Week 6
- Subject is persistently in poor compliance with study treatment or procedures
- The investigator formally unblinds the subject's treatment allocation

Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) and the 4-week SAE follow-up.

Subjects that discontinue study drug early will continue in the study (off study drug) and will be assessed at the subsequent visit(s) as described in the Time and Events visit schedule, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 26 visit. These off-treatment visits will include assessment and collection of:

- SAEs
- Specific AEs of interest (ie, MACE events, acute pancreatitis, and possible cases of thyroid neoplasm)
- Vital signs (including body weight)
- Concomitant medications

NOTE: Subjects randomly assigned to double-blind JNJ-64565111 or placebo only, will return to the investigational site approximately 5 weeks after the last dose of study drug for JNJ64565111/placebo-treated subjects and 4 weeks after the last dose of study drug for liraglutide-treated subjects to collect SAEs unless the subject has died, has been lost to follow-up, or has withdrawn consent. For subjects randomly assigned to double-blind JNJ-64565111 or placebo, blood samples will also be collected for PK and immunogenicity anti-drug antibody (ADA) measurement.

If subjects that discontinued study drug early are unable to return to their site for the scheduled on-site study visit, an alternate contact visit should be conducted with the goal of collecting any SAEs, MACE events (ie, CV death, nonfatal MI and nonfatal stroke), and AEs of thyroid neoplasm. Details regarding discussions via telephone, email, or other methods of contact must be properly documented on subject's source record and eCRF, including date of contact, outcome and responses provided by the subjects. The site may consult subjects' delegated contact(s) for the off-treatment follow-up if the site is unable to reach the subjects after multiple attempts.

Discontinuation from the Study

A subject will be discontinued from the study for any of the following reasons:

- Death
- Lost to follow-up
- Withdrawal of consent

When a subject is discontinued from the study, the reason for early study discontinuation is to be documented in the eCRF and in the source document. Study drug assigned to a subject who discontinued from the study may not be assigned to another subject. Subjects who discontinued from the study will not be replaced.

Lost to Follow-up

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. This should include repeated telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the sites should obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers), as well as other contact information (eg, email addresses) before randomization. In addition, the site should emphasize the importance of follow-up information to the subject before randomization. The measures taken to follow-up must be documented.

Withdrawal of Consent

Withdrawal of consent from the study by a subject should be a very unusual occurrence in a clinical trial. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence.

Withdrawal of consent in this trial may only be logged in the eCRF after a discussion between the investigator and the appropriate sponsor representative.

For subjects truly requesting withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses or is physically unavailable, the site should document the reason for the subject's failure to withdraw consent in writing.

If a subject had previously withdrawn consent from the study but decides to retract that withdrawal, the subject will be reconsented. The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Ethical Committee.

Withdrawal from the Use of Archive Samples in Future Research

The subject may withdraw consent for use of archive samples for future exploratory research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed and no further testing will take place after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

11.1. Analysis Sets

The intent-to-treat (ITT) analysis set will include all subjects who are randomly assigned to a treatment group and have a baseline measurement of body weight. The modified intent-to-treat (mITT) population includes all ITT subjects who had at least 1 post-baseline measurement of body weight within 7 days following a dose of study drug. The completers' analysis set will consist of all mITT subjects who have completed 26 weeks of double-blind treatment (ie, documented in the eCRF by the investigators that the subject has completed participation in the study through the Week 26 visit). The safety analysis set will include all randomized subjects who have received at least one dose of study drug.

The primary efficacy analysis, to demonstrate the superiority of JNJ-64565111 compared to placebo on percentage reduction in body weight from baseline to Week 26, as well as all secondary efficacy analyses, will be based on the mITT analysis set and will include only those measurements taken up to and including the last dose of study drug plus 7 days. A secondary analysis of the primary and secondary efficacy endpoints will be based on the ITT population. This analysis will include all measurements. Sensitivity analyses based on the completers' analysis set will also be performed for the primary endpoint.

Efficacy data will be analyzed according to the initial randomization assignment, regardless of the actual treatment received. Safety data will be analyzed according to the predominant treatment received, in the event that a subject receives a treatment other than that to which he/she is randomly assigned.

11.2. Sample Size Determination

A total of 440 subjects will be randomized into this study with 55 subjects per group allocated to placebo and JNJ-64565111 5.0 mg group, 110 subjects per group allocated to each of other 3 groups: JNJ-64565111 7.4 mg, JNJ-64565111 10.0 mg, open-label liraglutide 3.0 mg. Sample size was determined based on assessing the primary hypothesis that the treatment with

JNJ-64565111 for 26 weeks leads to greater percentage reduction in body weight compared with placebo as well as the exploratory hypothesis that the treatment with JNJ-64565111 leads to greater percentage reduction in body weight compared with open-label liraglutide.

Assuming a common standard deviation (SD) of 7% with respect to percent change in body weight at Week 26 and a 2-sided Type 1 error rate of 0.05, it is estimated that a sample size of 55 randomized subjects per group will have approximately 90% power to detect a treatment difference of 4.4%, 110 randomized subjects per group will have approximately 90% power to detect a treatment differences of 3.1%.

11.3. Efficacy Analyses

All hypotheses will be tested 2-sided at a 5% significance level unless otherwise specified.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage change in body weight between JNJ-64565111 and placebo from baseline to Week 26.

The primary efficacy endpoint will be analyzed based on the mITT analysis set using a mixed model for repeated measures (MMRM). The analysis will use the observed data through Week 26 while on treatment (up to the last dose of study drug plus 7 days) and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the fixed, continuous, covariates of baseline body weight and baseline-by-visit interaction. An unstructured covariance will be used to model the within-patient errors. The treatment comparisons will be made between each of the JNJ-64565111 treatment groups and placebo at Week 26 based on this model.

A secondary analysis of the primary endpoint will be based on the ITT population and will employ pattern mixture models using multiple imputation methods. Responses for subjects who discontinued from the study earlier than Week 26 will be imputed based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. The imputation will be done within groups defined by randomized treatment. Data will be analyzed using the same model as in the primary analysis. The treatment comparisons between each of the JNJ-64565111 treatment groups and placebo will be made at Week 26. Details of this approach will be provided in the SAP.

Finally, the primary efficacy endpoint will be analyzed based on the completers' analysis set. Additional analysis using a MCP-Mod (Multiple Comparison Procedure – Modeling) approach will be performed to explore the dose-response relationship.

The exploratory analysis of the assessments between the JNJ-64565111 treatment groups (7.4 mg and 10 mg) and liraglutide on the percentage change in body weight will also be performed. The same analysis model used for the comparisons with placebo on the primary efficacy endpoint will be used for these assessments.

Secondary Efficacy Endpoints

Secondary efficacy analyses at Week 26 will include proportion of subjects with ≥5% weight loss, proportion of subjects with ≥10% weight loss, and the absolute change in body weight from baseline.

The continuous secondary endpoints (ie, absolute change in body weight from baseline) at Week 26 will be analyzed with an MMRM model similar to the primary efficacy endpoint in the mITT analysis set.

The categorical secondary efficacy endpoint (ie, proportion of subjects with ≥5% weight loss, proportion of subjects with ≥10% weight loss at Week 26) will be analyzed longitudinally using a generalized linear mixed model. The model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline weight, and baseline-by-visit interactions. An unstructured covariance will be used to model the within-patient errors. The odds ratio and associated p-value for the treatment comparison between each of the JNJ-64565111 treatment groups versus placebo at Week 26 based on this model will be provided.

A secondary analysis of the secondary endpoints will be based on the ITT population and will employ pattern mixture models using multiple imputation methods based on information from retrieved dropouts as described above. For the categorical endpoints, response status will be determined from the imputed continuous response based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements.

The exploratory analysis of the assessments between the JNJ-64565111 treatment groups (7.4 mg and 10 mg) and liraglutide on ≥5% weight loss responders and ≥10% weight loss responders and the absolute change in body weight at Week 26 will also be performed. The same analysis models used for the comparisons with placebo will be used for these assessments.

Multiplicity Adjustment

The type I error will be strongly controlled at α=5% for each of primary endpoint and secondary endpoints. The Dunnett's method will be used to adjust the multiplicity of the comparisons of each of the JNJ-64565111 doses versus placebo for the primary efficacy endpoint of the percentage change in body weight and the secondary endpoint of the absolute change in body weight. The Bonferroni correction will be used to adjust the multiplicity of the comparisons for the secondary endpoints of the proportion of subjects with weight loss ≥5% and ≥10%.

Exploratory Endpoints

Exploratory endpoints of interest include the following to Week 26:

- the change in BMI from baseline
- the change in waist circumference from baseline
- the change in fasting lipids (total cholesterol, LDL-C, HDL-C, triglycerides) from baseline

- the change in FPG from baseline
- the change in fasting insulin from baseline
- the change in fasting C-peptide from baseline
- the changes in HOMA-B and HOMA-IR from baseline
- the change in SBP from baseline
- the change in DBP from baseline
- the change in pulse rate from baseline
- the change in pulse-pressure product from baseline
- in a subset of subjects participating in the 24-hour ABPM assessment, the changes from baseline in 24-hour SBP, DBP, pulse rate, and pulse-pressure product

Change from baseline in total cholesterol, LDL-C, HDL-C, triglycerides, fasting insulin, SBP, DBP, and pulse-pressure rate will be analyzed using a MMRM model similar to that used to analyze the primary efficacy endpoint.

The exploratory PRO endpoints will be summarized descriptively at baseline and over time. These endpoints include:

- IWQOL-Lite total, physical function, and self-esteem, sexual life, public distress, and work domain scores
- Ease of Weight Management total scores
- PAM total scores
- In English-speaking subjects in selected countries, ERCQ domain scores and PROMIS SF 8b total scores (Note: the PGIS and PGIC will be used to calculate responder definitions for the new instruments only and are not exploratory objectives.)
- In English-speaking subjects in selected countries, to describe pre-trial goals and expectations as well as post-trial experiences qualitatively using the ACTT Pre-trial interviews and a modified STEP exit interview

Summary qualitative findings from pre- and post-treatment interviews (ie, ACTT and STEP interviews, respectively) will also be provided.

11.4. Pharmacokinetic Analyses

Population PK analysis of serum concentration-time and exposure-response relationship data of JNJ-64565111 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-64565111 and included in the population PK analysis.

Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all subjects with available serum concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment group, descriptive statistics, including sample size (n), mean, standard deviation (SD), percent coefficient of variation (%CV), geometric mean, geo CV%, median, minimum, and maximum will be calculated for serum concentrations at each time for JNJ-64565111.

11.5. Immunogenicity Analyses

The incidence of anti-JNJ-64565111 antibodies will be summarized for all subjects who receive at least 1 dose of JNJ-64565111 and have appropriate samples for detection of antibodies to JNJ-64565111.

A listing of subjects who are positive for antibodies to JNJ-64565111 will be provided. The maximum titers of antibodies to JNJ-64565111 will be summarized for subjects who are positive for antibodies to JNJ-64565111.

The incidence of neutralizing antibodies (NAbs) to JNJ-64565111 will be summarized for subjects who are positive for antibodies to JNJ-64565111 and have samples evaluable for NAbs to JNJ-64565111.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

11.6. Safety Analyses

The evaluation of safety will be based on the incidence of AEs and changes in clinical laboratory test results and vital sign results (blood pressure, pulse rate). Summaries of AEs, clinical laboratory test results, and vital sign results will be provided by treatment group.

Adverse Events

The terms used in the eCRFs by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent adverse events [TEAEs]) will be included in the analysis.

For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. The percentage of subjects with specific TEAEs will be summarized by severity and relationship to study drug, as classified by the investigator, by treatment group. The dose-response relationship of dose levels on TEAE will be assessed, assuming that the incidence rates of TEAE will be monotonic with respect to dose levels. A listing for non-TEAEs will be provided.

Further analyses, to be described in the SAP for this study which will be finalized before the subject is randomized, will be conducted on the prespecified AEs for which additional information is collected from the investigators (see Section 9.10, Safety Evaluations), and on other AEs.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Normal reference ranges will be provided. Criteria for markedly abnormal laboratory values will be prespecified in the SAP. The percentage of subjects with markedly abnormal results will be summarized for each laboratory analyte. Descriptive statistics will be reported for each laboratory analyte at baseline and at each scheduled time point and for change from baseline.

Vital Signs and Physical Examination

Descriptive statistics of pulse rate and sitting blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical examination findings will not be summarized except when reported as an adverse event.

11.7. Interim Analysis

An interim analysis will be performed when approximately 90% of subjects have either completed or discontinued prior to approximately 10 weeks of study drug treatment. The objective of this interim analysis is to identify active treatment groups, if any, associated with safety or tolerability issues and to facilitate planning of the Phase 3 program.

An independent statistician and a programmer (who are not associated with the JNJ-64565111 obesity development program) responsible for providing the interim analysis results, as well as members of the internal DMC, will be unblinded to the individual treatment assignments during the conduct of the study. The unblinded individual subject data and interim analysis results will not be shared with investigators, subjects, or the sponsor staff who are involved in the conduct of the study before the final database lock. Details of the interim analysis will be provided in the DMC SAP.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in

conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

For AEs of interest, investigators may be asked to provide more detailed information on applicable supplemental forms or eCRFs. Adverse events of interest include MACE (ie, CV death, nonfatal MI and nonfatal stroke), hypotension-related AEs, pancreatic events (ie, AEs of pancreatitis, adverse event of serious or severe abdominal pain leading to suspicion of pancreatitis, and confirmed lipase or amylase elevations ≥3× ULN), calcitonin elevation, and thyroid neoplasm. If AEs of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-64565111, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For liraglutide, the expectedness of an AE will be determined by whether or not it is listed in the package insert.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the Serious Adverse Event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 5 weeks after the last dose of JNJ64565111/placebo or 4 weeks after the last dose of liraglutide, must be reported using the Serious Adverse Event Form. Anticipated events will not be recorded and reported in this study as to allow full reporting of AEs from these studies without any special reporting exceptions for individual case safety reports (ICSRs) of AEs. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible,

diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee (IEC) /IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

The cause of death of a subject in a study within 4 weeks of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). Product complaints defined above for devices that are approved marketed devices or commercially available medical devices will be directed to the specific product's manufacturer per the manufacturer's guidelines.

If the product quality issue relates to the safety injector, the device should be retained in the returns sharp container (also referred to as the evidence tube) provided to the subject. The subject is to return the sealed returns sharp container containing the safety injector to the site and the site is to ship it as directed by the sponsor for investigation.

If the product quality issue relates to the solution for injection and not to the device, the safety injector device should be retained in the returns sharp container (also referred to as the evidence tube) provided to the subject. The subject is to return the sealed returns sharp container containing the safety injector to the site. The site should maintain the safety injector for further investigation if requested by the sponsor and the site is to ship it as directed by the sponsor for investigation.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

JNJ-64565111 and Matching Placebo

JNJ-64565111 is a colorless solution, and is essentially free of visible particulate matter. JNJ-64565111 is supplied in pre-filled safety injectors containing nominal volumes of 0.25, 0.37, or 0.5 mL of 20.0 mg/mL JNJ-64565111 solution (5.0, 7.4, and 10.0 mg, respectively). Placebo for JNJ-64565111 will be supplied as pre-filled safety injectors containing matching volumes (ie, 0.25, 0.37, or 0.5 mL) of solution for SC injection. The pre-filled safety injector is intended for SC administration and consists of a syringe, a needle safety device, and grip accessory. Study drug will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Liraglutide

Commercially available supplies of liraglutide will be dispensed to subjects randomly assigned to the open-label liraglutide arm of the study. Liraglutide is formulated as a clear, colorless solution.

Each 1.0 mL of liraglutide solution contains 6.0 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14.0 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains 3.0 mL solution equivalent to 18.0 mg liraglutide (free-base, anhydrous).

14.2. Packaging

JNJ-64565111 and Matching Placebo

JNJ-64565111 and matching placebo will be packaged in individual kits. Each kit will consist of one pre-filled safety injector consisting of a syringe, a needle safety device, and grip accessory.

Liraglutide

Commercially available supplies of liraglutide will be dispensed to subjects randomly assigned to the open-label liraglutide arm of the study. Liraglutide is supplied as multi-dose pens, each pre-filled with 18.0 mg liraglutide/ 3.0 mL solution. Liraglutide will be repackaged in individual kits.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 36 to 46°F (2 to 8°C) and protected from light and heat.

Study drug must not be utilized after the expiry date printed on the label. JNJ-64565111 or matching placebo does not contain preservatives; therefore, any unused portion remaining in the safety injector must be discarded.

Refer to the study-site investigational product and procedures manual for additional guidance on study drug preparation, handling, administration and storage.

Liraglutide

Store new, unused liraglutide pens in the refrigerator at 36°F to 46°F (2°C to 8°C). Store the pen in use for 30 days at 59ºF to 86ºF (15ºC to 30ºC) or in a refrigerator at 36°F to 46°F (2°C to 8°C).

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form.

JNJ-64565111/matching placebo-treated subjects should be instructed to return the following:

- unused safety injectors

- empty study drug cartons
- study drug diary

Liraglutide-treated subjects should be instructed to return the following:

- unused pens
- used and partially used pens (without the needle)
- empty study drug cartons
- study drug diary

All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug returned by the subject, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used needles from liraglutide pens or used safety injectors containing residual liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned unused study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- IWRS Manual and worksheets
- Template ICFs
- eCRF completion guidelines
- Materials to promote healthy dietary and exercise habits
- Study drug diaries (ie, JNJ64565111/Placebo diary, liraglutide diary)
- IWQOL-Lite questionnaire

- single item Ease of Weight Management
- PAM
- 7-day ERCQ diary (selected sites)
- PROMIS SF 8b questionnaire (selected sites)
- PGIS questionnaire (selected sites)
- PGIC questionnaire (selected sites)
- Survey on Subject Satisfaction with Self-injection (selected sites)
- ACTT Pre-trial interviews; Modified STEP exit interviews, including training materials, recording devices, data collection forms for hand written notes, materials for mailing to vendor for qualitative analysis
- Laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study
- At selected sites, supplies for conducting 24-hour ABPM procedure
- ABPM diary (selected sites)
- PRO Completion Guideline

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This Phase 2b dose-ranging study is being conducted to assess the safety and efficacy of JNJ-64565111 over a 26-week period in non-diabetic obese subjects and to provide information to select JNJ-64565111 dose(s) to be assessed in Phase 3 studies.

The primary ethical concerns of this study are that the safety profile of JNJ-64565111 is not fully established and therefore subjects may be placing themselves at an increased risk of unexpected events by participating in this study. Although definitive information from studies in humans is not yet available, safety information from the Phase 1 studies indicates that JNJ-64565111 is generally well tolerated and no safety concerns precluding further clinical development have been identified.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. The investigator will be provided with detailed information about the study to ensure that the study research staff is fully informed.

Based on available data from preclinical and clinical JNJ-64565111 findings and known data from other GLP-1 agonists, potential adverse human effects may occur. These include increase in pulse rate, GI intolerability, pancreatitis, and elevation in calcitonin. Also, occasional increases in FPG and decrease in plasma sodium levels have been observed in subjects with T2DM treated with JNJ-64565111. In addition to the routine assessment of AEs, the following safety measures are included to monitor and address these potential effects: subjects with personal or family histories of MTC or MEN2A, active or chronic pancreatitis, and hepatic disease will be excluded from participating in the study, and those enrolled will undergo periodic monitoring of calcitonin, lipase/amylase, and liver enzymes. Specific monitoring algorithms are provided in case of elevations that warrant further follow-up and investigations in subjects experiencing prespecified elevation of these parameters.

In subjects with T2DM treated with metformin, the addition of JNJ-64565111 led to inconsistent changes in glycemic endpoints after 4-weeks of treatment, with some subjects experiencing increase in FPG and 24-hour mean glucose. While glucagon and GLP-1 agonism have counteracting effects on glucose control, dual agonism of GLP-1 and GCGR generally leads to improved glucose control in subjects with T2DM as the effects of GLP-1 to increase insulin secretion appear to overcome the effects of glucagon agonism to increase endogenous glucose production. However, it is possible that some subjects may be more sensitive to the glucagon agonism induced by JNJ-64565111 than to the GLP-1 agonism, and these subjects may have plasma glucose concentrations increased by treatment with JNJ-64565111. As subjects with severe obesity, such as those enrolled in this study, are at risk to develop prediabetes and diabetes over time, the glycemic status of all subjects enrolled will be monitored throughout the duration of study, and subjects with persistent glycemic elevation will be required to initiate treatment with metformin. Furthermore, in Study 64565111EDI1002 two subjects were reported to have AEs of hyponatremia in the context of dehydration or following episodes of vomiting. Few other subjects had mild reduction in plasma sodium levels not considered to be clinical meaningful by the reporting investigators. It is not known whether changes in plasma sodium are related to concomitant GI AEs (such as vomiting) or to other mechanisms. In the present study, electrolytes will be monitored frequently, and subjects with low sodium levels will not be allowed to participate in the study. In addition, those who develop persistent reductions in sodium levels will be permanently discontinued from study drug.

This study design includes the use of a placebo group, which is of key importance in helping to characterize both the safety and efficacy of JNJ-64565111. A study without a placebo arm cannot properly determine the weight-lowering efficacy of a weight-management medication. Similarly, given background occurrence of AEs in this population in which comorbidities are common, without a placebo, it is not possible to precisely define the safety and tolerability profile of a new treatment for obesity. Given the continuing need for new medications to improve the care of patients with obesity, providing a thorough evaluation of a medication such as JNJ-64565111 that may provide good efficacy and other useful benefits, is important. In considering the balance of risk to subjects allocated to the placebo group it is important to note that while obesity is associated with cardiovascular morbidity and mortality it is commonly not treated pharmacologically. Liraglutide (Saxenda®) is included as an active comparator as it is the

only GLP-1 receptor agonist approved for the treatment of obesity. As JNJ-64565111 and liraglutide both act on the GLP-1 receptor but JNJ-64565111 also acts on the GCGR the comparison of the efficacy, tolerability and safety is an important assessment in this study. The liraglutide arm of the study is open-label because the product is purchased commercially and has a characteristic injection device that would not allow masking. As described above, all subjects including those on placebo will receive diet and exercise counseling from a trained counselor.

Women of childbearing potential enrolled in the study and who are sexually active must agree to use a highly effective birth control method (failure rate of <1% per year when used consistently and correctly) throughout the study. Serum pregnancy testing will be performed on all women of childbearing potential at screening and EOT, in addition to selected time points during the study at the discretion of the investigator. Women must also agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study or for a period of at least 4 weeks after the last dose of study drug.

Clinical and laboratory evaluations will be performed throughout the study (according to the Time and Events Schedule) to monitor the safety of subjects. Subjects who discontinue early from the study will have a post-study visit, to allow collection of information on SAEs, and support a complete assessment of key safety events in the intact randomized study population.

The approximate maximum blood volume that would be collected if a subject were to complete the 4-week follow-up visit after the Week 26 /EOT visit will be approximately 176.0 mL in subjects randomly assigned to JNJ-64565111 or matching placebo, and approximately 137.5 mL in subjects randomly assigned to the open-label liraglutide treatment arm. The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study; it is less than the amount of blood in a standard blood donation (ie, <500 mL over 60 days) (American Red Cross).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded

by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study for archive samples for future exploratory research may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-64565111, to understand obesity, to understand differential drug responders, and to develop tests/assays related JNJ-64565111 and obesity. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the PI

- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the PI, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto-query (generated by the eDC tool).

- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit/contact for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit/contact at that study site, 3 days after the subject's visit/contact (query generation and resolution excluded), or in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-64565111 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-64565111, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: New York Heart Association Classification of Cardiac Disease

The following table represents the NYHA classification of cardiac disease:

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Attachment 2: Method of Blood Pressure and Pulse Rate Measurement

Subject Preparation

The subject should remove all clothing that covers the location of cuff placement. (The sleeve should not be rolled up so that it has a tourniquet effect.)

The subject should be comfortably seated with legs uncrossed, and back and arm supported, so that the upper arm is at the level of the right atrium (midpoint of the sternum).

The subject should be instructed to relax and not talk; approximately 5 minutes should pass before the first reading is taken.

Blood Pressure Measurement Device

Blood pressure readings should be taken manually with a mercury sphygmomanometer or an automated blood pressure monitor. If an automated blood pressure monitor is used, the pulse rate reading provided by the device can be used as the subject's pulse rate measurement.

Cuff Size

A cuff should be chosen that is appropriate for the individual, based upon the upper arm circumference in centimeters. The bladder of the cuff should encircle at least 80% of the arm circumference.

Arm Circumference (cm)	Size
22-26	Small Adult
27-34	Adult
35-44	Large Adult
45-52	Adult Thigh

For the subject with an arm circumference over 50 cm when a thigh cuff cannot be fitted over the arm, an appropriately-sized cuff should be placed on the subject's forearm, the forearm should be supported at heart level, and the radial pulse at the wrist should be used.

Cuff Placement

Palpate the brachial artery in the antecubital fossa.

Place the midline of the bladder of the cuff so that it is over the arterial pulse on the subject's bare upper arm. The lower end of the cuff should be 2 to 3 cm above the antecubital fossa to allow space for the stethoscope.

Pull the cuff snugly around the bare upper arm. Neither the observer nor the subject should talk.

Inflation/Deflation

Inflate the cuff to at least 30 mmHg above the point at which the radial pulse disappears. Deflate the mercury column at 2 to 3 mmHg per second.

The first and last audible sounds should be taken as systolic and diastolic pressure.

Number of Measurements

Three readings should be taken at intervals of at least 1 minute apart, and the results recorded.

Blood pressure should be measured at the screening visit in both arms. If there is an inter-arm difference of more than 10 mmHg in either the systolic or diastolic pressure, the arm with the higher pressure should be used for all subsequent blood pressure measurement during the study.

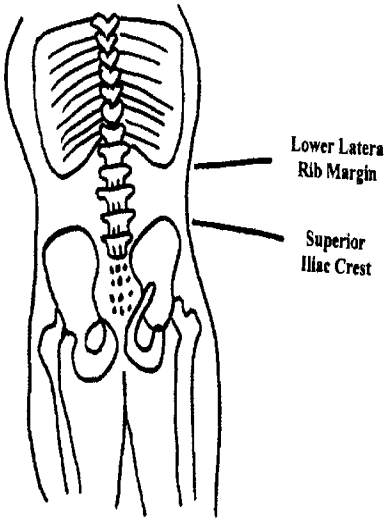
If possible, if the blood pressure is measured manually, it should be taken by the same individual, using the same equipment, at each visit so as to reduce inter-observer variability (Pickering 2005).

Attachment 3: Anthropometric Measurements

Height will be measured using a wall-mounted stadiometer or one mounted on a balance beam scale, whichever is most appropriate for the individual subject. Subjects should be wearing socks or barefoot and should not be wearing shoes.

Body weight will be measured using a calibrated scale. Subjects should be weighed wearing underwear and a gown; they will be instructed to take off their shoes and to empty their bladders before being weighed. The scale should be calibrated according to the manufacturers specifications and at the frequency recommended by the manufacturer before the first subject is weighed. Calibration must be documented in the calibration log.

Waist circumference will be measured with the subject standing, wearing underwear, with or without a gown. The measurement will be performed at a level midway between the superior aspect of the iliac crests and the lower lateral margin of the ribs (refer to diagram below). The measurement need not be at the level of the umbilicus. The measuring tape will be kept horizontal.



Patient Standing, tape horizontal at level between Left Lateral Rib Margin and Superior Iliac Crest

Attachment 4: Standardized Nonpharmacologic Weight Reduction Therapy

At randomization (ie, Day 1), trained counselors will utilize standard educational materials to deliver a counseling session. This session will assist the counselors in providing subjects with a variety of diet and physical activity tools to help subjects incorporate healthy practices into their daily lives. Subjects will be provided with user-friendly and interactive subject support materials. Subject support materials contain educational insight into the topic area, specific action steps to improve lifestyle habits, and interactive exercises that make it easy for each subject to think through and apply.

General patient education materials will be supplied to support diet counseling. Study sites are encouraged to provide diet and physical activity information (eg, pamphlets or brochures or other such material) relevant to the local country or region.

a. Weight Loss Diet

The energy level of the prescribed diet will be 600 kcal (2,083 kilo Joules [kJ]) less than the individual subject's calculated total energy expenditure, and should have:

- <10% of calories per day derived from added sugars
- <10% of calories per day derived from saturated fat
- <2.3 g of sodium per day

Basal metabolic rate (BMR) is estimated as kilocalories per day by means of the Harris-Benedict equation.*

- For men: 66.473 + (5.003 x height [cm]) + (13.752 x weight [kg]) – (6.755 x age)
- For women: 655.096 + (1.850 x height [cm]) + (9.563 x weight [kg]) – (4.676 x age)
- Total energy expenditure is estimated as: BMR*1.3 (correction factor for mild to moderate activity)

* Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, DC: Carnegie Institute of Washington; 1919:Publication 279.

Attachment 5: Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and urine samples for urinalysis will be collected at timepoints specified in the Time and Events Schedule. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF and take appropriate action (eg, repeating abnormal laboratory result or further evaluation as considered clinically appropriate). The following tests will be performed by the central laboratory.

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -magnesium
  -chloride
  -bicarbonate
  -uric acid
  - blood urea nitrogen
  -creatinine
  -aspartate aminotransferase
  -alanine aminotransferase
  -gamma-glutamyltransferase
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase
  -lactic acid dehydrogenase
  -amylase
  -lipase
  -calcium
  -phosphate
  -albumin
  -total protein

- Serum ß-hydroxybutyrate
- Serum calcitonin
- Fasting insulin*
- Follicle-stimulating hormone only for women >45 years of age with amenorrhea for at least 6 months and <18 months prior to screening
- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol) *
- HbA_{1c}
- Fasting plasma glucose*
- Urinalysis

  Dipstick done at central laboratory
  -specific gravity
  -protein
  -ketones
  -urobilinogen
  -leukocyte esterase
  -pH
  -blood
  -bilirubin
  -nitrite
  If dipstick result is abnormal, microscopic examination will be performed.

- Serum (β-human chorionic gonadotropin [β-hCG] pregnancy testing will be conducted for all women of childbearing potential (ie, unless they are permanently sterilized or unless there is a documented history of their postmenopausal status) at the screening and Week 26/EOT visits. Additional serum or urine pregnancy tests may be performed throughout the study in sufficient number, as determined

necessary by the investigator, or required by local regulation, to establish the absence of pregnancy during the study.

* Subjects must be fasting for at least 8 hours before blood sample collections.

Estimated Glomerular Filtration Rate (eGFR)

- The estimated glomerular filtration rate (eGFR) will be reported according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation** at study visits when serum creatinine is measured. The CKD-EPI equation based on serum creatinine, age, sex, and race for adults age ≥18 years expressed as a single equation is:

CKD-EPI Formula (for S_{cr} expressed in mg/dL)

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

$\kappa = 0.7$ for females
$\kappa = 0.9$ for males
$\alpha = -0.329$ for females
$\alpha = -0.411$ for males
min = the minimum of S_{cr}/κ or 1 max = the maximum of S_{cr}/κ or 1

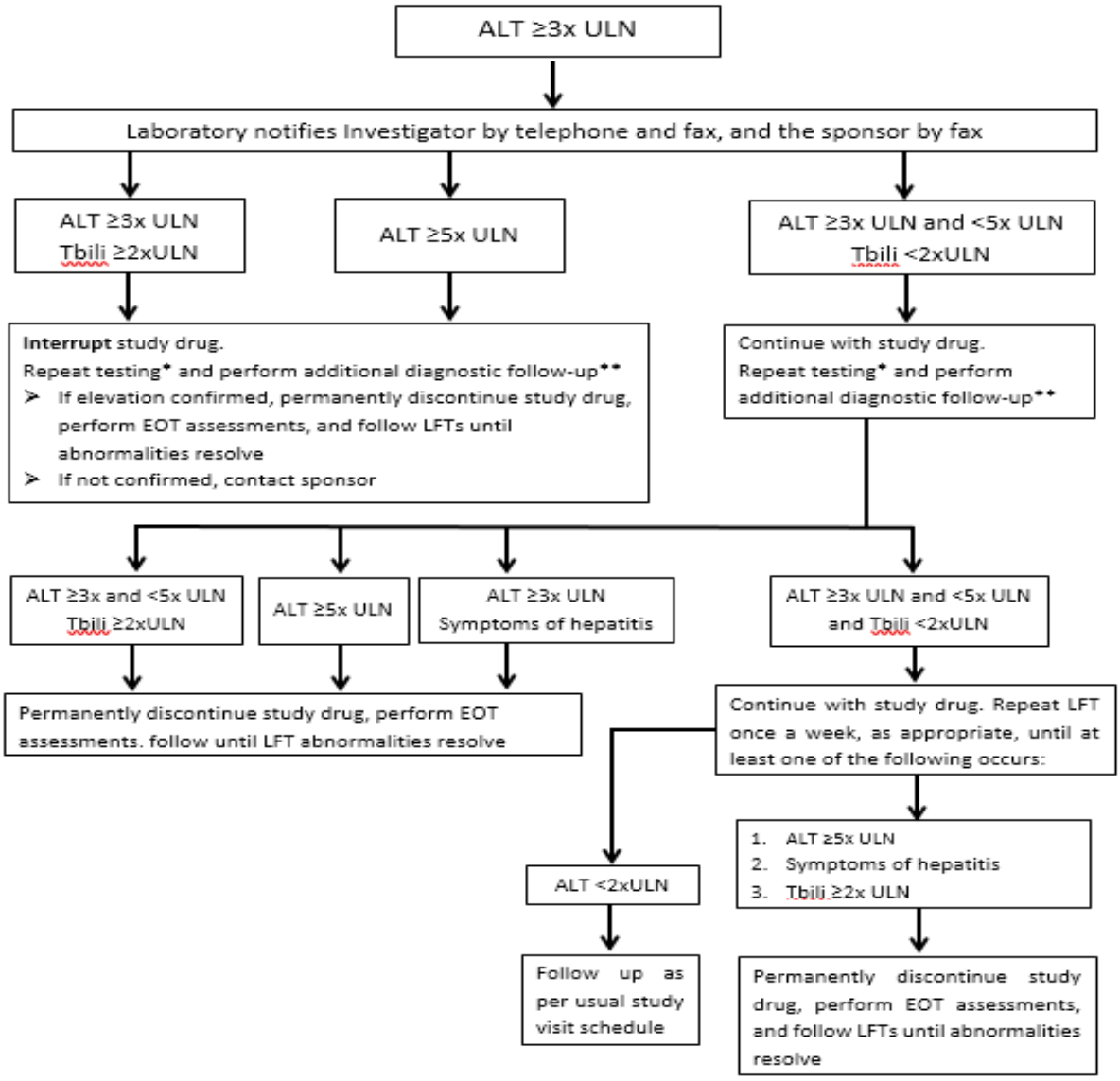
CKD-EPI Formula (for S_{cr} expressed in μmol/L)

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

$\kappa = 61.9$ for females
$\kappa = 79.6$ for males
$\alpha = -0.329$ for females
$\alpha = -0.411$ for males
min = the minimum of S_{cr}/κ or 1 max = the maximum of S_{cr}/κ or 1

**Levey AS, Stevens LA, Schmid CH, et.al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). Ann Intern Med. 2009;150(9):604-12.

Attachment 6: Algorithm for Monitoring Abnormal Liver Function Tests



If the investigator feels that the subject cannot safely continue administration of study drug regardless of the algorithm, the subject should discontinue study drug and continue to the EOT visit.

Key: ALT=alanine aminotransferase; EOT=End-of-Treatment; LFT=liver function test; Tbili=total bilirubin; ULN=upper limit of normal

* LFT (ie, ALT, AST, total bilirubin, alkaline phosphatase, GGT) within 2 to 3 days of investigator receipt of report, with earlier testing (ie, within 1 day of receipt of laboratory report) for more substantial elevations in ALT (≥5xULN) or total bilirubin (≥2xULN) levels

** Focused medical history (including review of prior history of liver or biliary disorders, concurrent symptoms, review of all concomitant medications [eg, acetaminophen-containing medications, over-the-counter or herbal medications, nutritional supplements] including any changes in medications, detailed review of alcohol use; liver ultrasound and follow-up imaging as appropriate; hepatitis serology (anti-HAV, HBsAg, anti-HBs, anti-HB core, anti- HCV, HCV RNA, EBV and CMV screen) and autoantibodies (eg, ANA, anti-smooth muscle antibody) should be obtained as appropriate, with additional evaluation as clinically indicated. The extent of the evaluations should be made in consultation with the sponsor.

Attachment 7: Pancreatitis Monitoring and Withdrawal Criteria

All subjects will be carefully monitored for pancreatitis during the study. Investigators will urge subjects to make an appointment for an unscheduled visit if the subject experiences persistent nausea and/or vomiting for ≥3 days, with or without abdominal pain.

Blood samples for analysis of serum amylase and lipase by a central laboratory should be obtained at the visit, and other additional investigations should be performed in order to establish diagnosis, per investigator's discretion.

Study drug should be interrupted immediately if any of the following circumstances occur at any time during treatment:

- If pancreatitis is suspected, or
- Serum amylase ≥2x ULN, or
- Serum lipase ≥2x ULN.

The pancreatic enzyme tests should be repeated within 7 days after the first sample (with both samples analyzed by the central laboratory), and appropriate imaging tests should be performed to establish diagnosis. The results of these tests should be recorded in the source documents.

All subjects with elevated pancreatic enzymes should be followed-up with multiple serum amylase and lipase tests until resolution.

Study drug should be discontinued if acute pancreatitis is confirmed, based on at least 2 of the following 3 signs or symptoms:

- characteristic abdominal pain,
- amylase and/or lipase >3x ULN, or
- characteristic findings on CT/MRI.

In any of the circumstances described above occur during the study, the investigator must complete the AE/SAE eCRF page and a Pancreatitis Adverse Event of Special Interest Form. If the event meets the SAE criteria, the information will be transmitted to the sponsor using the Serious Adverse Event Form within 24 hours of the repeat laboratory test.

If a subject discontinues study drug according to the Pancreatitis Monitoring and Withdrawal Criteria then, the event should be recorded as an AE and the reason for withdrawal should be documented as an AE. The subject should be followed to a satisfactory conclusion (ie, until the adverse event resolves, the laboratory value returns to baseline, or the condition becomes stable).

Attachment 8: Guidelines for Calcitonin Monitoring

Calcitonin ≥10 ng/L and <20 ng/L

Confounders that can affect calcitonin measurements should be taken into consideration before aggressive diagnostic procedures are undertaken for subjects with CT 10 to < 20 ng/L at the screening visit. Specific history should be elicited to identify these confounders. Confounders (ie, drugs [H2 blockers, proton pump inhibitors (PPIs)] other causes of hypergastrinemia [eg, pernicious anemia], smoking, autoimmune thyroiditis, presence of heterophilic antibodies) should be factored into the interpretation of the values on a case-by-case basis. If drugs can be discontinued safely, the screening calcitonin can be repeated after a wash-out period. Calcitonin levels return to the normal range by ~ 10 days after stopping PPIs.

Calcitonin ≥20 ng/L

All calcitonin values ≥20 ng/L will be flagged on the laboratory reports from the central laboratory and will be submitted to the sponsor and study site. Subjects will have to undergo a repeat measurement. The timing of the repeat measurement will depend on when the calcitonin value ≥20 ng/L was first observed. In particular:

- calcitonin ≥20 ng/L on Day 1/Randomization visit: a repeat measurement of calcitonin should be performed preferably within 7 days.
- calcitonin ≥20 ng/L at any time after Day 1/Randomization: a repeat measurement of calcitonin should be performed preferably within 2 weeks.

If the repeat calcitonin is confirmed to be ≥20 ng/L, the event "elevated calcitonin" should be reported as an AE of interest.

Depending on the degree of the confirmed calcitonin elevation, additional clinical management or diagnostic procedures should be performed. In particular:

Calcitonin ≥20 ng/L and <50 ng/L

Subjects with calcitonin levels in this range at baseline Day 1 or subsequent visits should have the measurement repeated for confirmation per the suggested window period outlined above. This cohort will provide valuable insights into any potential effect that JNJ-64565111 may have on calcitonin levels in subjects with values above the normal range at baseline. If the repeat value or if any subsequent value measured during the trial is ≥50 ng/L then the subject moves into the evaluation category listed above for values ≥50 ng/L.

Calcitonin ≥50* ng/L and <100 ng/L

If subjects develop a calcitonin value within this specified range post-randomization, specific medical evaluation will be indicated including a thyroid ultrasound and a pentagastrin stimulation test if available and if not contraindicated (Note: pentagastrin is contraindicated in subjects with known coronary artery disease). Those subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. In the US, where pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

A repeat determination should be performed within 2 weeks if serum calcitonin value ≥50 pg/mL (≥50 ng/L) after baseline and the study drug treatment should be permanently discontinued if the repeat determination confirms that the serum calcitonin value remains ≥50 pg/mL (≥50 ng/L).

Calcitonin ≥100* ng/L

For any value of ≥100 ng/L, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid. Diagnostic evaluation should consist of thyroid ultrasound, fine needle aspiration of any nodules >1 cm and potentially surgery with neck dissection. Family history of MTC or MEN2 should be evoked and a rearranged during transfection (RET) proto-oncogene analysis should be undertaken.

* A repeat determination should be performed within 2 weeks if serum calcitonin value ≥50 pg/mL (≥50 ng/L) after baseline and the study drug treatment should be permanently discontinued if the repeat determination confirms that the serum calcitonin value remains ≥50 pg/mL (≥50 ng/L).

NOTE: pg/mL is the conventional unit and ng/L is the SI unit.

Attachment 9: Instructions for the Completion of PRO Assessments

The following instructions are intended to assist investigators, study coordinators, and those with monitoring responsibilities with the accurate completion of all the PRO questionnaires. For some sites, PRO questionnaires will be completed during scheduled site visits while other PRO questionnaires will be completed at home by the subject. It is therefore important for sites to be familiar with the PRO Time & Events schedule to ensure subjects complete the PROs at the correct setting and visit. Please refer to the PRO Completion Guideline for further information.

Site Responsibilities (General)

For this study, we expect that it will take approximately 20 minutes for the subjects to be trained and complete the PROs that are intended to be completed during site visits. For those PROs that are intended to be completed at home, it will take subjects less than 5 minutes a day to complete.

General:

- Never copy PROs from other sources (eg, websites); use only the PRO diaries provided.

Site visit-based assessments, sites must:

- Ensure subject completes the PROs before any clinical assessments are done or results are provided.
- Please have the subject complete the PROs in the same order each time.

Home-based assessments, sites must:

- Ensure subject understands what is expected of them when they return home.
- Distribute the PRO home diaries and have the subject review to see if they have questions.
- Have the subject complete the PROs in the order that they appear in the diary.
- Remind the subject to return the PRO home diary at their next scheduled visit.

Preparing the Subject

General:

- Instruct subjects to complete all PRO questionnaires using a blue or black ballpoint pen.
- Explain that all the information on the PROs is confidential, and that someone from the study staff will only check for completeness and not share the results with other clinical staff.
- Explain to subjects the reasons why they are being asked to complete the PROs, ie, they are part of the overall medical assessment and are designed to find out more information about how having their disease has affected their life.
- Allow as much time as the subject needs to orient themselves and complete all PROs.
- Instruct the subjects to:
  - Read the instructions for each questionnaire carefully.
  - Note the recall period for each questionnaire.
  - Complete all PROs; Instruct the subject not to skip any questions/or questionnaires.
- Subjects must interpret questions and complete the PROs without input from anyone. If asked for help interpreting or completing the PROs by the subject, please simply reply that there are no right or wrong answers and he/she should use his/her best judgment to complete each question (based on what the subject thinks the question is asking).

- Do not attempt to interpret or explain the instructions, questions, or response options.
- If the subject has difficulty choosing between 2 response options, simply state "choose the answer that most closely matches your experience."

Site visit-based assessments:

- Provide a quiet, private or semi-private location for the subject to complete the PROs.
- Ensure subjects have access to study staff for questions.

Home-based assessments:

- Instruct the subject to complete each daily assessment at the same time each day, in the same setting each day, for the following 7 consecutive days.
- These questionnaires are administered at home because of the concepts being measured and the period of recall.

Quality Control

- Complete the subject number, visit date and time on every PRO questionnaire.

Site visit-based assessments:

- Before the subject leaves:
  - Check for any questions that might have been skipped/left blank.
  - If an item has been skipped, point this out to the subject and ask them to complete.
  - If an item has more than one response, ask the subject to reconsider the question and try to choose the answer that most closely matches their experience.

Home-based assessments:

- Before the subject leaves the appropriately scheduled site visit, distribute the PRO home diary, provide instructions for completion, and remind subject to return the booklet at the next scheduled site visit.
- Questionnaires in the diary should be completed by the subject daily for the next 7 consecutive days.
- Upon the subject's return for their next scheduled site visit, collect the PRO home diary from the subject and check for completeness.

Special Issues

- Subjects should be instructed to complete the PROs without input from anyone. However, if a subject cannot read the PROs or complete it/them independently (eg, due to visual impairment, limited literacy, or difficulty with pens), then a designated person can read the items and response choices aloud and mark the appropriate response choices as verbally stated by the subject.
- The designated person should read each question in its entirety in a neutral voice, avoiding any cues, even if interrupted by the subject with an answer. The designated person should repeat each of the subject's answers, eg, "A little bit." The subject should not be prompted by the designated person in any other way. No help should be offered to the subject in interpreting the questionnaire.
- If a person is designated to assist the subject with the PROs, this person should remain consistent across assessment questionnaires and across assessment periods.
- If a designated person assists the subject with the PROs, this should be noted in the Footer section on the first page of each PRO assessment instrument.

INVESTIGATOR AGREEMENT

JNJ-64565111 (efinopegdutide)
Clinical Protocol 64565111OBE2001– Amendment 1

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Maria Alba, MD

Institution: Janssen Research & Development

Signature: [redacted] Date: 23 August 2018

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 23 August 2018