Janssen Research & Development *

Clinical Protocol

Protocol Title

A Randomized, Double-blind Placebo-controlled, Parallel-group, Multicenter, Dose-ranging Study to Evaluate the Safety and Efficacy of JNJ-64565111 in Severely Obese Subjects with Type 2 Diabetes Mellitus

Short Title

Evaluation of JNJ-64565111 in Severely Obese Subjects with Type 2 Diabetes Mellitus

Protocol 64565111OBE2002; Phase 2b
AMENDMENT 1

JNJ-64565111

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).]

Status: Approved
Date: 23 August 2018
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-156156741, 2.0

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	05 April 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, to add a discontinuation criterion for subjects who experience severe vomiting, and to correct minor errors.

Applicable Section(s)	Description of Change(s)
Rationale: To add a discontinuation criterion about vomiting.	
Section 7.1, Discontinuation from Study Drug	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 provide further instructions on the management of subjects with adverse events of moderate and severe vomiting that may lead to dehydration.	
Section 8.2, Safety Assessments	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 fix minor errors.	
Section 5.2, Exclusion Criteria	Fixed exclusion criterion No, 10 from "the screening visit" to "Week -2 visit."
Section 7.1, Discontinuation from Study Drug	Fixed sub-bullet that should be stand-alone bullet (ie, "Subject has persistent 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" is now separate from the eGFR criterion).
Section 8.1, Efficacy Assessments	Corrected when IWQOL-Lite will be administered (ie, from "Weeks -1" to "Weeks -2."
Appendix 6, Method of Blood Pressure and Pulse Rate Measurement	Updated text about blood pressure measurements.

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind Placebo-controlled, Parallel-group, Multicenter, Dose-ranging Study to Evaluate the Safety and Efficacy of JNJ-64565111 in Severely Obese Subjects with Type 2 Diabetes Mellitus (T2DM)

JNJ-64565111 (formerly designated as HM12525A, developed by Hanmi Pharmaceuticals) is a synthetic, modified oxyntomodulin (OXM) peptide; it is the site-specific form of HMGLP/GCG25 (a glucagon-like peptide-1 [GLP-1]/glucagon dual agonist peptide), that is conjugated to the constant region of a human immunoglobulin G4 fragment (HMC001) via a 10 kDa polyethylene glycol linker.

In vitro, JNJ-64565111 stimulates both GLP-1 and glucagon receptor (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. JNJ-64565111 lowers cholesterol, low-density lipoprotein (LDL), and triglycerides in animal models of dyslipidemia.

OBJECTIVES AND ENDPOINTS

Primary Objectives

The primary objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese T2DM subjects after 12 weeks of treatment on:

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

Secondary Objectives

The secondary objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese T2DM subjects after 12 weeks of treatment on:

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

Exploratory Objectives

The exploratory objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese T2DM subjects after 12 weeks of treatment on:

- the proportion of subjects with ≥10% weight loss from baseline
- the change in body mass index (BMI) from baseline
- the change in waist circumference from baseline
- the change in glycated hemoglobin (HbA_{1c}) 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
- the change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides) from baseline
- pharmacokinetic (PK) exposure
- the change in scores on the Impact of Weight on Quality of Life – Lite (IWQOL-Lite) from baseline
- the change in scores on the Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function Short Form 10a (PROMIS SF 10a) from baseline
- the change in scores on the Eating-related Concept Questionnaire (ERCQ) from baseline

Hypotheses

In severely obese subjects with T2DM, treatment for 12 weeks with JNJ-64565111 compared with placebo leads to:

Primary:

- Greater percentage reduction in body weight from baseline

Secondary:

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

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, 4-arm, multicenter study in severely obese subjects with T2DM. Subjects who are ≥18 and ≤70 years of age and have a BMI ≥35 kg/m2 to ≤50 kg/m2 are eligible to participate if they have a HbA_{1c} of ≥6.5% to ≤9.5% at the screening visit on diet and exercise alone or on a stable dose of a single oral antihyperglycemic agent (AHA) or dual-combination oral AHAs for ≥12 weeks prior to screening.

NUMBER OF SUBJECTS

A target of 188 subjects will be randomly assigned in this study.

TREATMENT GROUPS AND DURATION

On Day 1, subjects who continue to meet eligibility criteria, will be randomly assigned in a 1:1:1:1 ratio to blinded treatment with placebo or JNJ-64565111 5.0 mg, 7.4 mg, or 10 mg and enter a 12-week treatment phase. Post-randomization visits will be conducted at Week 2, 6, 12/end-of-treatment [EOT] visit, and the follow-up visit 5 weeks after the last dose of study drug. At Weeks 4 and 10, 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).

Counseling should be done by dietitians/nutritionists on Day 1 to provide assessment and recommendation on a reduced-calorie diet and exercise regimen. In addition, subjects will be counseled on maintaining proper hydration throughout the study especially in circumstances of potential dehydration (eg, nausea and vomiting). At subsequent visits (Week 2 and Week 6), counseling and reinforcement of the recommended diet/exercise and hydration regimens will be conducted by a trained counselor. In addition, beginning at Week -2 visit, subjects will be counseled to comply and perform fasting self-monitored blood glucose (SMBG) testing at least 2 times per week. At each treatment visit, the investigator or qualified, assigned designee will review the subject's diaries, concomitant medications and the adverse events (AEs) that started or changed since the last visit.

Study Drugs Administered

Open-label AHA Background Therapy

Subjects on oral AHA will be required to have been on a stable treatment regimen (ie. same agent and same dose) for at least 12 weeks prior to screening and to remain on such regimen throughout the remainder of the study.

Antihyperglycemic agents allowed at screening and as glycemic rescue medication during study are: metformin, sulphonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and thiazolidinediones (TZDs).

Basal insulin is not allowed at screening but can be used as a glycemic rescue medication.

On days of protocol-specified study visits, subjects are to withhold their morning dose of subjects' oral AHA until after the completion of all study visit procedures.

JNJ-64565111/Placebo During Run-in Period

At the Week -2 visit, subjects will be instructed on the use of prefilled safety injectors to perform subcutaneous (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 once weekly SC injections are eligible to participate in the study. To assess compliance with the dosing regimen, eligible subjects will be dispensed prefilled safety injectors containing 0.5 mL open-label placebo and instructed to perform self-injections once weekly at home during the run-in phase, as well as keep a study drug diary of their injection schedule.

Double-blind JNJ-64565111 or Matching Placebo During Double-Blind Treatment Period

JNJ-64565111 will be supplied as a solution for injection at a concentration of 20 mg/mL. Blinded study drug will be provided in prefilled safety injectors with attached SC needle, prefilled 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. The prefilled 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.

On Day 1, subjects randomly assigned to the double-blind treatment arms will receive a supply of their randomly-assigned study drug 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.

Drug Administration

Subjects will be instructed to administer study drug SC once weekly for the entire duration of the 12-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 days proceed in the next quadrant in a counterclockwise manner.

Injections can be done at any time of day irrespective of meals. However, it is preferable that study drug be injected during the same overall time period of the day on a week-to-week basis.

Study drug 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, and should mark a calendar to ***remind*** them of when to take the next weekly dose. Subjects will 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 to the time of study-drug dosing. The information will be entered into electronic case report forms (eCRFs) by the site personnel.

Subjects 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 study drug 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.

Glycemic Rescue Medication

During the 12-week treatment phase, glycemic rescue therapy will be implemented in subjects with FPG values (repeated and confirmed within 7 days) meeting the prespecified criteria. Subjects should be counseled to contact the site if their fasting SMBG consistently (ie, ≥3 days within a week) exceeds 200 mg/dL, and an FPG measurement to determine eligibility for glycemic rescue therapy should be obtained. Subjects should have reinforcement of diet and exercise recommendations before obtaining the repeat FPG value. At the investigator's discretion, based upon recent fasting SMBG values that are consistent with the initial FPG result meeting glycemic rescue criteria, this single FPG (ie, without a repeat FPG value) may be used to demonstrate eligibility for glycemic rescue therapy.

Rescue therapy may include increasing the dose of a current AHA or the initiation of a new AHA. Investigators will manage rescue therapy, including the selection of the specific AHA, its clinically appropriate initial dose and titration regimen (if applicable), the need to switch from one AHA rescue medication to another (eg, poor glycemic response to prior rescue medication), and be consistent with the labeled use within the country of the study site. Metformin, sulphonylureas, TZDs, SGLT-2 inhibitors, DPP-4 inhibitors, and insulin (basal only) are allowed as rescue medication. GLP-1 agonists and short-acting or intermediate insulins are not allowed as rescue medications.

EFFICACY EVALUATIONS

The primary efficacy endpoint will be the percentage change in body weight from baseline to Week 12 between JNJ-64565111 compared with placebo.

The secondary measures of efficacy at Week 12 include proportion of subjects with ≥5% weight loss from baseline, and the absolute change in body weight from baseline.

Exploratory efficacy endpoints at Week 12 include proportion of subjects with ≥10% weight loss from baseline, change from baseline in BMI, waist circumference, HbA_{1c}, FPG, fasting insulin, fasting C-peptide, HOMA-B, HOMA-IR, fasting lipids (ie, total cholesterol, LDL-C, HDL-C, triglycerides), SBP, DBP, pulse rate, pulse-pressure product, PK exposure, and patient-reported outcomes (PROs) (ie, changes in IWQOL-Lite, PROMIS SF 10a, and ERCQ).

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected from all subjects according to the Schedule of Activities for determination of serum trough concentrations of JNJ-64565111 to assess attainment of steady-state concentrations. In addition, a non-trough (peak) sample on Day 4 will be collected from all subjects, as well as a post-treatment sample at 16 weeks from all subjects.

IMMUNOGENICITY EVALUATIONS

Anti-JNJ-64565111 antibodies will be evaluated in serum samples collected from all subjects according to the Schedule of Activities.

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, calcitonin, lipase, amylase, hematology, and urinalysis), physical examination including complete skin examination, serum/urine pregnancy testing, electrocardiogram (ECG), SMBG, assessment of hypoglycemia episodes, and review of concomitant medications.

STATISTICAL METHODS

A total of 188 subjects will be randomly assigned in this study with 47 subjects per group allocated to each of the 4 treatment groups. Sample size was determined based on assessing the primary hypothesis that treatment with JNJ-64565111 at 1 or more dose levels for 12 weeks leads to greater percentage reduction in body weight compared with placebo.

Assuming a common standard deviation (SD) of 4% with respect to percent change in body weight at Week 12 and a 2-sided type I error rate of 0.05, it is estimated that a sample size of 47 randomly assigned subjects per group will have approximately 90% power to detect a treatment difference of 2.7%.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage change in body weight between JNJ-64565111 and placebo from baseline to Week 12.

The primary efficacy endpoint will be analyzed based on the modified intent-to-treat (mITT) analysis set using a mixed model for repeated measures (MMRM). The analysis will use the observed data through Week 12 while on treatment (up to the last dose of study drug plus 7 days) and prior to rescue medication. The analysis model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the 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 12 based on this model.

A secondary analysis of the primary endpoint will be based on the intent-to-treat (ITT) analysis set and will employ pattern mixture models using multiple imputation methods. This analysis will use all observed data, including the measurements off treatment. Responses for subjects who discontinued from the study earlier than Week 12 will be imputed based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. The imputation will be done within randomized treatment groups. 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 12. 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 Multiple Comparison Procedure – Modeling approach will be performed to explore the dose-response relationship.

Secondary Efficacy Endpoints

Secondary efficacy analyses at Week 12 will include the absolute change in body weight from baseline and the proportion of subjects with ≥5% weight loss.

The absolute change in body weight from baseline at Week 12 will be analyzed with an MMRM model similar to the primary efficacy endpoint based on the mITT analysis set.

The proportion of subjects with ≥5% weight loss will be analyzed longitudinally using a generalized linear mixed model (Multiple Comparison Procedure – Modeling) based on the mITT analysis set. The analysis will use the observed data through Week 12 while on treatment (up to the last dose of study drug plus 7 days) and prior to rescue medication. The model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous 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 12 based on this model will be provided.

A secondary analysis of the secondary endpoints will be based on the ITT analysis set and will employ pattern mixture models using multiple imputation methods based on information from retrieved dropouts as described above. For the proportion of subjects with ≥5% weight loss, response status will be determined from the imputed continuous response based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements.

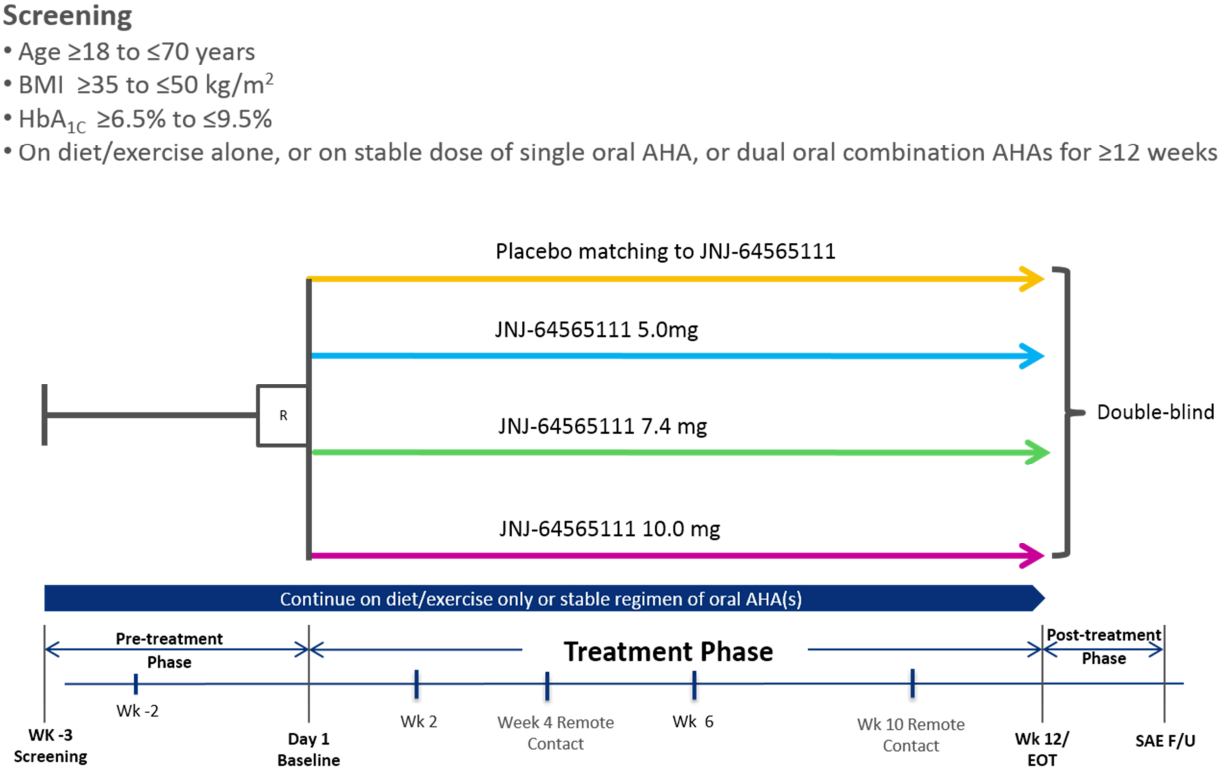
Safety Analyses

The evaluation of safety will be based on the incidence of AEs and hypoglycemia episodes, and changes in clinical laboratory test results and vital sign results (blood pressure, pulse rate). The safety analyses will be based on the safety analysis set including all data, regardless of the initiation of glycemic rescue therapy (ie, including data after initiation of rescue therapy). Additional analysis of hypoglycemia will be performed based on the data prior the initiation of glycemic rescue therapy only. Summaries of AEs, clinical laboratory test results, and vital sign results will be provided by treatment group. There will be no imputation of missing values for clinical safety laboratory test results, and vital sign measurements.

1.2. Schema

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Protocol Activity	Pre-treatment			Treatment Phase								Post-treatment
	Screening	Run-In										
	Wk -3	Wk -2	Wk-1	Day 1 (Randomization)	Day 4	Wk 2	Wk 4 (RC)[a]	Wk 6	Wk 10 (RC)[a]	Wk 11	Wk 12/ EOT[b]	SAE Follow-Up[c]
Screening/Administrative												
Informed consent [d]	X											
Inclusion/exclusion criteria	X	X		X								
Medical history & demographics	X											
Prior therapy reporting and review [e]	X	X		X								
IWRS log-in	X	X		X		X		X			X	
Randomization				X								
Study Drug Administration												
Show and/or describe injection device		X										
Dispense run-in medication		X										
Dispense double-blind medication				X		X		X				
Injection at study site [f]		X		X								
Dispense study drug diary		X		X		X		X				
Review study drug diary				X		X		X			X	
Run-in compliance assessment				X								
Drug return and accountability				X		X		X			X	
Survey on self-administration of study drug [g]								X				
Clinical Procedures												
Physical examination [h]	X										X	
Vital signs (PR and BP, in triplicate) [i]	X			X		X		X			X	
Weight [j]	X			X		X		X			X	
Height	X											
Waist circumference [j]				X							X	
12-lead ECG (local)		X										
Laboratory Assessments [k]												
Fasting fingerstick glucose [l,m]				X								
Glycated hemoglobin (HbA_{1c})	X			X		X		X			X	
Fasting plasma glucose (FPG)[l]	X			X		X		X			X	
Fasting C-peptide [l]	X			X							X	
Fasting insulin [l]				X							X	
Fasting lipid profile [l]	X			X							X	
Serum chemistry	X			X		X		X			X	

Protocol Activity	Pre-treatment			Treatment Phase								Post-treatment
	Screening	Run-In										
	Wk -3	Wk -2	Wk-1	Day 1 (Randomization)	Day 4	Wk 2	Wk 4 (RC)[a]	Wk 6	Wk 10 (RC)[a]	Wk 11	Wk 12/ EOT[b]	SAE Follow-Up[c]
Hematology	X			X							X	
Calcitonin	X			X							X	
Serum β-hydroxybutyrate				X		X		X			X	
Urine dipstick/urinalysis				X							X	
Serum pregnancy test [n]	X										X	
Urine pregnancy test				X[o]								
Follicle-stimulating hormone [p]	X											
Trough Pharmacokinetic and Immunogenicity Anti-Drug Antibodies samples [q]				X		X		X			X	X
Non-trough Pharmacokinetic sample					X							
Fasting plasma, serum, and urine archive samples for exploratory research [l]				X							X	
Patient-Reported Outcomes [r]												
IWQOL-Lite		X									X	
Dispense diary containing Eating-related Concepts Questionnaire (ERCQ)		X						X				
Contact subjects to remind completion of the 7-day ERCQ diary									X			
Completion of 7-day ERCQ diary			X----------X[s]							X----------X[s]		
PROMIS Physical Function Short Form (PROMIS SF 10a)		X		X							X	
Patient Global Impression Status (PGIS)		X[t]									X[t]	
Patient Global Impression of Change (PGIC)											X[t]	
Subject Counseling and Ongoing Review/Assessments												
Diet/exercise and hydration counseling and reinforcement [u]				X		X		X				
SMBG and hypoglycemia counseling [v,w]		X										
Dispense glucose meter, test strips, and blood sugar diary [w]		X		X		X		X				
Record SMBG level, hypoglycemic episodes, and concomitant medications [x, e]		X	X	X	X	X	X	X	X	X	X	
Review/discuss blood sugar diary (which includes SMBG results, hypoglycemia events, and concomitant medications)		X		X		X		X			X	

Protocol Activity	Pre-treatment			Treatment Phase								Post-treatment
	Screening	Run-In										
	Wk -3	Wk -2	Wk-1	Day 1 (Randomization)	Day 4	Wk 2	Wk 4 (RC)[a]	Wk 6	Wk 10 (RC)[a]	Wk 11	Wk 12/ EOT[b]	SAE Follow-Up[c]
Adverse Event reporting and review [y]		X		X	X	X	X	X	X	X	X	X

AE=adverse event; AHA=antihyperglycemic agent; BP=blood pressure; ECG=Electrocardiogram; eCRF=electronic case report form; EOT=end-of-treatment; ERCQ=Eating-related Concepts Questionnaire; FPG=Fasting plasma glucose; FSH=Follicle-stimulating hormone; HbA_{1c}= Hemoglobin A_{1c}; HR=heart rate; IWQOL-Lite=Impact Of Weight On Quality Of Life-Lite; IWRS=interactive web response system; PK=Pharmacokinetics; PROMIS SF 10a=Patient-Reported Outcomes Measurement Information System Physical Function Short Form 10a; RC=remote contact; SAE=serious adverse event; SMBG=Self-monitored blood glucose; Wk=Week.

a) Study-site staff will contact subjects preferably by telephone to reinforce the adherence to diet and exercise, proper hydration, study drug dosing reminder, assessment of subjects' status, and compliance with the protocol procedures (eg, diary completion reminder).
b) 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 Schedule of Activities, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 12 visit. These off-treatment procedures will include assessment and collection of SAEs, specific AEs of interest (ie, major adverse cardiac events, acute pancreatitis, and possible cases of thyroid neoplasm), vital signs (including body weight), and concomitant medications.
c) The SAE follow-up visit will be conducted for all subjects approximately 5 weeks after the last dose of study drug to collect serious adverse events since the last visit unless the subject has died, has been lost to follow-up, or has withdrawn consent. Blood samples will also be collected for PK and immunogenicity (ie, anti-drug antibody) measurement. Subjects who prematurely discontinue study drug for any reason prior to Week 12 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.
d) Informed Consent must be signed at the screening visit before any study procedures are performed.
e) Record any medications taken from up to 30 days before screening (and up to 6 months before screening for AHA) until the first dose of treatment phase study drug on Day 1 (baseline) as prestudy therapy in the corresponding eCRF. Concomitant therapy includes all medications taken since the first dose of treatment phase study drug on Day 1.
f) 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.
g) A survey will be given to English-speaking subjects to assess subject satisfaction with the experience of self-administering JNJ-64565111 or matching placebo.
h) Physical examinations will include a full review of body systems including a complete skin examination. Physical examination abnormalities noted after the baseline assessment will be collected if considered an adverse event by the investigator (recorded on adverse event eCRF). In addition to the physical examination required at the screening visit and EOT visit, investigators should use their clinical judgment whether additional physical examinations (either full of focused) are needed (eg, subject reporting injection site reaction, flank pain, pedal edema, etc.).
i) Blood pressure and pulse rate: 3 seated readings will be recorded in the source and eCRF. See Appendix 6, Method of Blood Pressure and Heart Rate Measurement.
j) 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 Appendix 5, Anthropometric Measurements.
k) Specific details about specimen collection, storage, packaging, and shipping will be provided in an operations manual from the central laboratory.
l) Subjects must fast for at least 8 hours before blood sample collection. For fasting samples to be collected at the screening visit, if subject is not fasting, 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.
m) Fasting fingerstick glucose values may be obtained by study-site staff at the study site or by the subject at home on the morning of Day 1.

n) 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 5.1, Inclusion Criteria) at the screening and Week 12/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.
o) Urine pregnancy test must be negative before dosing can proceed. In the case of an ambiguous test result, a serum pregnancy test will be performed and randomization will be delayed by a few days in order to obtain the test result. Randomization may only proceed if the result of the serum pregnancy test is negative.
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) All patient-reported outcome 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 Schedule of Activities, or at the time the subject discontinues the study drug, before all other evaluations, as specified in the Schedule of Activities. Assessments (whenever possible) should be completed before any tests, procedures, or discussion of AEs or the subject's medical condition. Refer to Appendix 13 for more details.
s) ERCQ diary should be completed at home for 7 consecutive days at these time points: (1) between day after Week -2 and day before Day 1 for 7 consecutive days and (2) between the day after Week 10 contact reminder and day before Week 12.
t) Patient Global Impression Status (PGIS) and Patient Global Impression of Change (PGIC) are needed to calculate responder definitions for new patient-reported outcome instruments ERCQ and PROMIS SF 10a. These are not exploratory efficacy endpoints.
u) Subjects will be counseled to maintain a diet and exercise regimen consistent with those outlined in treatment guidelines for T2DM (eg, the American Diabetes Association guideline). In addition, subjects will be counseled on maintaining proper hydration throughout the study especially in circumstances of potential dehydration (eg, nausea and vomiting).
v) Subjects will be instructed to return with their completed diaries to the study site for review by study-site personnel at each clinic visit (eg, for review of hypoglycemic events, insulin dosage changes [only for subjects who are on insulin], SMBG values, concomitant medications, timing of study drug taken and any missed doses of study drug).
w) Subjects will be provided with and instructed on the use of a home blood glucose monitoring system. Blood glucose testing supplies will also be provided as necessary.
x) Hypoglycemic episodes should be recorded on the hypoglycemia eCRF and also on the Adverse Event eCRF if considered an adverse event by the investigator (see Appendix 8 – Hypoglycemia: Definitions, Symptoms, and Treatment).
y) Adverse events will be monitored throughout the study from the time of signing the informed consent form until 5 weeks after the last dose of study drug.

2. 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 health-related 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 $\geq$40 kg/m^2) were associated with a nearly 2-fold, 3-fold, and 4-fold, respectively, greater probability of having at least 1 cardiometabolic risk factor (Nichols 2017). Hence, subjects with severe obesity (BMI$\geq$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-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 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 (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 the constant region of a human immunoglobulin G4 fragment (HMC001) via a 10 kDa polyethylene glycol 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. 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.

2.1. Study Rationale

JNJ-64565111 has been studied in a first in human study consisting of a single- and multiple-ascending dose study in overweight/obese subjects with and without T2DM for up to a 4-week period. In addition, 2 other multiple ascending dose studies were conducted in overweight/obese subjects with T2DM for 4 weeks to further assess higher doses and a different dosing regimen. Across all studies, 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 12-week period in severely obese subjects with T2DM being treated with diet and exercise alone or on a stable dose of single oral antihyperglycemic agent (AHA) or dual-combination oral AHA(s) for ≥12 weeks prior to screening. This information can then be used to select JNJ-64565111 dose(s) to be assessed in Phase 3 studies.

2.2. Background

Nonclinical Studies

Pharmacologic Profile

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 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, reduced 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 at a 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 the vehicle range except for the night periods where increases compared with the 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 the 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 that 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, genotoxicity studies, and pivotal embryo-fetal development studies were conducted in compliance with Good Laboratory Practices.

No mutagenic effects were detected with JNJ-64565111 during in vitro and in vivo genotoxicity studies. In embryo-fetal development studies, JNJ-64565111 was not teratogenic in rats at up to 4 nmol/kg, whereas this high dose in rabbits caused major external and underlying skeletal abnormalities primarily affecting the skull and limbs.

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. 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. In addition, 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 changes in organs 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. Findings in the rat 26-week toxicity study (0, 3, and 10 nmol/kg/week for 26 weeks, and at 20 and 30 nmol/kg/week for only 7 weeks because of the poor condition of the animals) were consistent with those in the shorter term 4-week rat study, were attributed to dose-related sequelae of exaggerated pharmacology, and showed evidence of reversibility during the 6-week recovery period. The NOAEL was considered to be 3 nmol/kg/week. At the NOAEL, Week 26 exposure in male and female rats corresponded to a maximum concentration (C_{max}) of 9.09 and 10.13 nmol/L, and an area under the curve in the interval 0–168 hours (AUC_{168hr}) of 1,271 and 1,261 h.nmol/L, respectively.

JNJ-64565111 was generally well tolerated in a monkey4-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. In the 16-week study in cynomolgus monkeys (0, 15, 25, and 40 nmol/kg/week), administration of JNJ-64565111 resulted in exaggerated pharmacological effects of body weight loss and/or poor body weight gain that led to secondary erythrocytic and clinical chemistry changes. Significant neutralizing ADA development with clearance of JNJ-64565111 in the majority of animals impacted the overall toxicological assessment, as few animals had continuous exposure to study drug. Based on minimal to slight pathological changes, mainly of the pancreas and liver tissues, and persistent weight loss predominantly at 40 nmol/kg/week, the NOAEL was 25 nmol/kg/week.

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 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.

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.

Clinical Studies

Clinical experience with JNJ-64565111 includes a first in human study (ie, HM-OXM-101) and two 4-week 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 pharmacokinetic (PK) data after repeated doses compared with 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 64565111 (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.

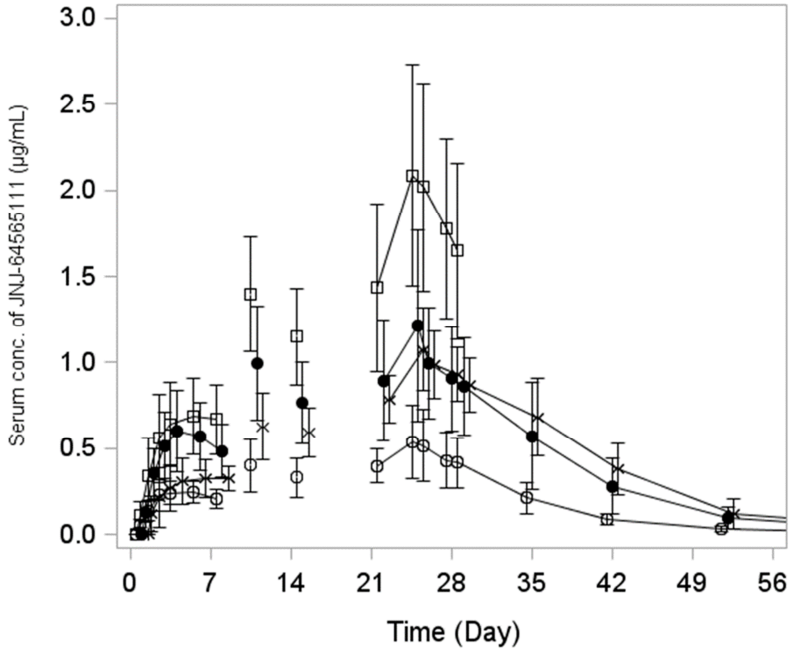
The PK parameters in the ongoing Study 64565111EDI1002, where the full range of JNJ-64565111 was studied using a fixed dose rather than weight-based dose showed that following the first dose of JNJ-64565111 of 5 to 15 mg, the mean (± standard deviation [SD]) JNJ-64565111 C_{max} ranged from 0.259 (0.072) 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.

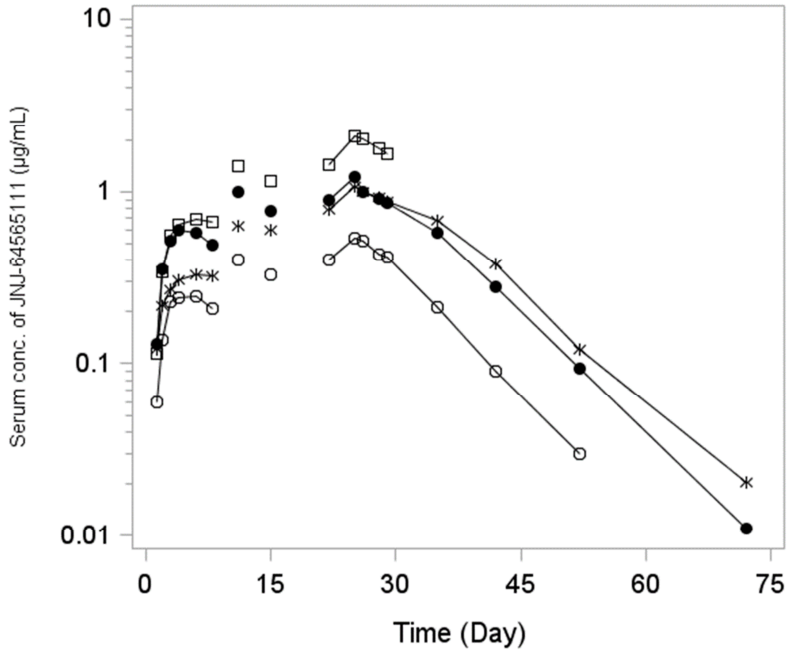
The mean accumulation ratio calculated as the ratio of Week 4 AUC_{τ} versus Week 1 AUC_{168h} was 2.33 to 4.01 for the 5 to 15 mg dose range, indicating moderate accumulation of JNJ-64565111 exposure upon multiple dosing that was commensurate with the dosing interval and $t_{½}$ of JNJ-64565111 ($t_{½}$=6 to 7 days in Study 64565111EDI1002). The mean JNJ-64565111 trough serum concentrations on Days 8, 15, 22, and 29 (Figure 2) 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 2: Mean (SD) Serum Concentration-time Profiles Following Multiple Subcutaneous 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)

Key: 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 serious adverse event (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. In general, there was a consistent trend of increase in pulse rate and decrease in systolic blood pressure (SBP) and diastolic blood pressure (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 (least square 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 mm Hg (least square 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 with a 1.3 bpm increase on placebo. Both SBP and DBP decreased by a mean of 11.8 and 4.2 mm Hg, 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 mm Hg 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 with 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 with 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 with 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 mmol/L (-12.8 mg/dL) in placebo. In the ongoing Study 64565111EDI1002, in which the mean baseline HbA_{1c} was higher compared with 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 with 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 with 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).

2.3. Benefit/Risk Assessment

Potential Benefits

The currently available pharmacologic treatments for obesity provide modest weight loss and are limited in use by tolerability. Although bariatric surgery represents the most effective treatment option currently available, it is typically reserved for only patients who have a BMI $\geq$40 kg/m^2 or $\geq$35 kg/m^2 with at least 1 serious obesity-related comorbidity. Bariatric surgery has been shown to provide significant short-term weight loss; however, uncertainty remains about long-term complication rates and the sustainability of weight loss and comorbidity control. Thus, 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 (Ettaro 2004; Jonsson 2002; Padwal 2003).

JNJ-64565111 stimulated both GLP-1R and GCGR with generally similar in vitro potencies. As a dual agonist, it can be an attractive treatment option for obese and obese diabetic patients based on its pharmacological effects such as body weight loss and blood glucose-lowering. The underlying synergistic mechanisms that mediated the effects of JNJ-64565111 on body weight loss observed in rodents were probably combined effects on energy intake and energy expenditure. In addition, the potential blood glucose-raising effects of JNJ-64565111 mediated by its glucagon-stimulating activity were likely efficiently counter-regulated by its GLP-1 activity, as JNJ-64565111 lowered blood glucose levels in db/db mice and during an intraperitoneal glucose tolerance test in diet-induced obese mice.

Clinical evidence of weight loss with JNJ-64565111 treatment has been shown in initial Phase 1 studies, with an observed 2% to 6% body weight reduction after 4 weeks across the dose range compared with a decrease of approximately 1% in subjects who received placebo. In addition, treatment with JNJ-64565111 was associated with decreases in mean values for total cholesterol, LDL-C, and triglycerides. There was also a consistent mean reduction in HbA_{1c} values from baseline after 4 weeks in the treatment groups compared with no change or a slight increase in the placebo group. Overall, these data suggest that treatment with JNJ-64565111 could lead to meaningful weight reduction along with an improvement in other metabolic parameters.

Potential Risks

Based on available data from nonclinical and clinical JNJ-64565111 findings and known data from other GLP-1 agonists, potential adverse human effects may occur. These include increase in HR, GI intolerability, pancreatitis, and elevation in calcitonin. 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 medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2), active or chronic pancreatitis, and hepatic disease will be excluded from participating in the study, and those enrolled will undergo periodic monitoring of pancreatic and liver parameters (through laboratory tests), thyroid changes (through monitoring of calcitonin levels and physical examination of the thyroid), vital signs (through periodic measurements of blood pressure and HR), and assessment of selected cardiovascular events (ie, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke). Specific monitoring algorithms are provided in case of elevations that warrant further follow-up and investigations in subjects experiencing prespecified elevation of these parameters.

Hypoglycemia is a common AE in patients with T2DM and may occur more frequently following weight loss. Treatment with JNJ-64565111 in the Phase 1 studies did not appear to lead to an increase in hypoglycemia. As part of study-specific glycemic monitoring, subjects will be provided with a glucose meter and will be instructed to collect fasting self-monitored blood glucose (SMBG) values. Subjects will be counseled on the signs and symptoms of hypoglycemia and instructed to measure their blood glucose and seek appropriate treatment for any potential episode of hypoglycemia. Reports of potential events of hypoglycemia will be carefully collected and evaluated.

In subjects with T2DM treated with metformin in the Phase 1 studies, the addition of JNJ-64565111 led to inconsistent changes in glycemic endpoints after 4 weeks of treatment, with some subjects experiencing an 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. Subjects will be instructed to contact the site if their fasting SMBG values are consistently elevated. Additionally, FPG from the clinic visits that meet prespecified and progressively more stringent glycemic rescue cut-offs will be defined for the investigators. During the study, if a subject's FPG values meet these thresholds and no readily identifiable cause of worsened glycemic control is evident, then the subject will receive glycemic rescue medication.

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, 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. Although ketones can increase in the blood and urine under physiological conditions in subjects with and without diabetes and is termed “ketosis,” under certain circumstances, ketones can accumulate to high levels and lead to an acidic state, termed “ketoacidosis,” which is associated with significant illness and metabolic decompensation, requiring emergent medical attention. While ketoacidosis is known to occur in patients with type 1 diabetes (ie, diabetic ketoacidosis [DKA]), patients with T2DM can on very rare occasion develop ketoacidosis, especially in the absence of inadequate carbohydrate intake and insulin deficiency (either absolute or relative due to increased insulin resistance observed in acute illness). A 2- to 3-fold increase in the serum levels of the ketone, β-hydroxybutyrate (generally <1.0 mmol/L), 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 JNJ-64565111 which would be expected given the weight loss observed and the dual agonism of JNJ-64565111 at the GLP-1 and glucagon receptors. Importantly, in these 2 studies conducted in subjects with T2DM, no AEs of ketoacidosis or metabolic acidosis were reported. Therefore, subjects receiving JNJ-64565111 may develop ketosis due to reduced food intake/weight loss, but it is unlikely, although theoretically possible, that they could develop DKA under certain conditions. Subjects with signs and symptoms of DKA should have appropriate laboratory evaluations (eg, blood pH, serum ß-hydroxybutyrate, anion gap) performed. Subjects who develop biochemically confirmed DKA will be permanently discontinued from study drug.

In Study 64565111EDI1002, two subjects were reported to have AEs of hyponatremia in the context of dehydration or following episodes of vomiting. A 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.

Risk-Benefit Ratio and Risk Mitigation

Overweight and obesity are a worldwide epidemic and a significant health issue. As noted previously, it is estimated that worldwide obesity has nearly tripled since 1975, affecting more than 650 million adults (WHO 2017). Pharmacological treatment options are limited, have variable degrees of efficacy, which is not necessarily sustained, and are associated with a range of potential safety or tolerability issues. Additional clinical data are needed to assess whether JNJ-64565111 could be a well-tolerated treatment for severe obesity.

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. Clinical and laboratory evaluations will be performed throughout the study (according to the Schedule of Activities) to monitor the safety of subjects. Potential risks will be managed and minimized by appropriate protocol eligibility criteria, subject management procedures, specific discontinuation criteria, and careful internal safety monitoring.

More detailed information about the known and expected benefits and risks of JNJ-64565111 may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objectives

The primary objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese T2DM subjects after 12 weeks of treatment on:

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

Secondary Objectives

The secondary objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese T2DM subjects after 12 weeks of treatment on:

- the absolute change in body weight from baseline

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

Exploratory Objectives

The exploratory objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese T2DM subjects after 12 weeks of treatment on:

- the proportion of subjects with ≥10% weight loss from baseline
- the change in BMI from baseline
- the change in waist circumference from baseline
- the change in glycated hemoglobin (HbA_{1c}) 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 SBP from baseline
- the change in DBP from baseline
- the change in pulse rate from baseline
- the change in pulse-pressure product from baseline
- the change in fasting lipids (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], and triglycerides) from baseline
- pharmacokinetic (PK) exposure
- the change in scores on the Impact of Weight on Quality of Life – Lite (IWQOL-Lite) from baseline
- the change in scores on the Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function Short Form 10a (PROMIS SF 10a) from baseline
- the change in scores on the Eating-related Concept Questionnaire (ERCQ) from baseline

ENDPOINTS

Primary Endpoint(s)

The primary efficacy endpoint will be the percentage change in body weight from baseline to Week 12 between JNJ-64565111 compared with placebo.

Secondary Endpoint(s)

The secondary measures of efficacy at Week 12 include the absolute change in body weight from baseline and the proportion of subjects with ≥5% weight loss from baseline.

Exploratory Endpoint(s)

Exploratory efficacy endpoints at Week 12 include proportion of subjects with ≥10% weight loss from baseline, change from baseline in BMI, waist circumference, HbA_{1c}, FPG, fasting insulin, fasting C-peptide, HOMA-B, HOMA-IR, fasting lipids (total cholesterol, LDL-C, HDL-C, triglycerides), SBP, DBP, pulse rate, pulse-pressure product, PK exposure, and patient-reported outcomes (PROs) (ie, changes in IWQOL-Lite, PROMIS SF 10a, ERCQ).

Refer to Section 8, Study Assessments and Procedures, for evaluations related to endpoints.

HYPOTHESIS

In severely obese subjects with T2DM, treatment for 12 weeks with JNJ-64565111 compared with placebo leads to:

Primary:

- Greater percentage reduction in body weight from baseline

Secondary:

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

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, 4-arm, multicenter study in severely obese subjects with T2DM. Subjects who are ≥18 and ≤70 years of age and have a BMI ≥35 kg/m^2 to ≤50 kg/m^2 are eligible to participate if they have a HbA_{1c} of ≥6.5% to ≤9.5% at the screening visit on diet and exercise alone or on a stable dose of single oral AHA or dual-combination oral AHAs for ≥12 weeks prior to screening. A target of 188 subjects will be randomly assigned in this study.

Subjects meeting all enrollment 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, subjects who continue to meet eligibility criteria, will be randomly assigned in a 1:1:1:1 ratio to blinded treatment with placebo or JNJ-64565111 5.0 mg, 7.4 mg, or 10 mg and enter a 12-week treatment phase. Post-randomization visits will be conducted at Week 2, 6, 12/end-of-treatment [EOT] visit, and the SAE follow-up visit 5 weeks after the last dose of study drug. At Weeks 4 and 10, 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).

During the pretreatment/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 12/EOT along with a urine pregnancy test at Day 1 in women of childbearing potential.

Counseling should be done by dietitians/nutritionists on Day 1 to provide assessment and recommendation on a reduced-calorie diet and exercise regimen (Appendix 7, Standardized Nonpharmacologic Weight Reduction Therapy). In addition, subjects will be counseled on maintaining proper hydration throughout the study especially in circumstances of potential dehydration (eg, nausea and vomiting). At subsequent visits (Week 2 and Week 6), counseling and reinforcement of the recommended diet/exercise and hydration regimens will be conducted by a trained counselor. In addition, beginning at Week -2 visit, subjects will be counseled to comply and perform fasting SMBG testing at least 2 times per week. 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 serum chemistry, calcitonin, lipase, amylase, hematology, and urinalysis), physical examination including complete skin examination, serum/urine pregnancy testing, ECG, SMBG, assessment of hypoglycemia episodes, and review of concomitant medications. Refer to Section 8.2, Safety Assessments, 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 SAE follow-up visit. 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 Schedule of Activities table, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 12 visit. These off-treatment visits will include collection of SAEs, specific AEs of interest (ie, major adverse cardiac events [MACEs], acute pancreatitis, and possible cases of thyroid neoplasm), vital signs (including body weight), and concomitant medications. All subjects, except those who died, were lost to follow-up, or have a withdrawn consent, will have a follow-up visit at least 5 weeks after the last dose of study drug was taken to collect any SAEs and blood samples for PK and immunogenicity ADA assessments will be obtained.

The ERCQ is a home-based assessment in contrast to the IWQOL-Lite, PROMIS SF 10a, Patient Global Impression Status (PGIS), and Patient Global Impression of Change (PGIC), which are site-based assessments.

Subjects who withdraw from the study will not be replaced.

During the 12-week treatment phase (Day 1 to Week 12), subjects meeting protocol-specified glycemic rescue criteria will have rescue therapy initiated, and will remain in the study, continuing double-blind study drug. Rescue therapy may include increasing the dose of a current AHA or the initiation of a new AHA. Investigators will manage rescue therapy, including the selection of the specific AHA, its clinically appropriate initial dose and titration regimen (if applicable), the need to switch from one AHA rescue medication to another (ie, poor glycemic response to prior rescue medication), and be consistent with the labeled use within the country of the study site. Metformin, sulphonylureas, thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin (basal only) are allowed as rescue medication; GLP-1 agonists and short-acting or intermediate insulins are not allowed as rescue medication.

The overall study duration is approximately 19 weeks and comprises of 3 phases:

- Pretreatment phase: 3 weeks comprised of:
  - Screening phase: 1 week
  - Run-in (injection-training) phase: 2 weeks
- Treatment phase (double-blind)
  - Placebo-controlled treatment phase: 12 weeks
- Post-treatment phase (SAE follow-up visit): 4 weeks

Approximately 188 subjects will be randomly assigned in a 1:1:1:1 ratio to one of the following once weekly SC treatments:

- 47 subjects to double-blind placebo matching JNJ-64565111,
- 47 subjects to double-blind JNJ-64565111 5.0 mg,
- 47 subjects to double-blind JNJ-64565111 7.4 mg,
- 47 subjects to double-blind JNJ-64565111 10 mg.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

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, Control, Study Phase/Periods, 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.

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 prefilled 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 12 weeks, which should be sufficient to capture statistically significant weight-loss effects of the active doses relative to placebo and provide information on the trajectory of the weight loss for each treatment group. The follow-up phase is designed to assess safety by collecting data on SAEs or resolution of ongoing SAEs that occurred since the last study visit, as well as collection of PK and ADA samples approximately 5 weeks after the last dose of study drug.

Study Population

The randomized study population consists of men and women, ages 18 to 70 years at screening, inclusive, with severe obesity (BMI ≥35 to ≤50 kg/m^2) and T2DM (ie, HbA_{1c} of ≥6.5% to ≤9.5% at screening) treated with either diet/exercise alone or with single or dual oral AHA regimen. 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). Consistent with Health Authority guidance, this study is being conducted in obese subjects with T2DM to understand the magnitude of weight loss and to assess any unique safety issues (eg, hypoglycemia) in this population. Given the potential contribution of weight loss on HbA_{1c}-lowering, the study will provide experience in severely obese subjects across a broad spectrum of different diabetes treatment regimens.

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 and exploratory endpoints are also consistent with the current FDA and EMA guidelines for the development of weight-management drugs and will provide further information on the magnitude and proportion of subjects experiencing weight loss along with any potential impact on other weight related comorbidities (ie, glycemic control, vital signs, lipids), and PROs.

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.

Choice of Patient-Reported Outcome Measures

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 health-related quality of life and physical functioning in this study (ie, IWQOL-Lite, PROMIS SF 10a, PGIS, and PGIC). The ERCQ will also be administered to measure eating-related concepts such as hunger, appetite, cravings, and satiety. These exploratory PRO endpoints will be used to describe outcomes/benefits associated with weight loss and treatment from a subject's perspective.

Collection of Additional Information for Selected Adverse Events

For selected adverse events of interest as per Health Authority guidance and based on class of effects of GLP-1 agonists and potential mechanistic physiological effects of glucagon receptor agonism, 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 include selected hypotension-related adverse events, adverse events of pancreatitis, calcitonin elevation, thyroid neoplasm, and episodes of hypoglycemia.

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 biomarkers 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 biomarkers (not prespecified) that could help to further explain and examine the efficacy and safety findings in this study.

4.2.1. Study-Specific Ethical Design Considerations

This Phase 2b dose-ranging study is being conducted to assess the safety and efficacy of JNJ-64565111 over a 12-week period in severely obese subjects with T2DM and to provide information to select JNJ-64565111 dose(s) to be assessed in Phase 3 studies.

The primary ethical concern of this study is 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. As discussed in Section 2.3, Benefit/Risk Assessment, clinical and laboratory evaluations will be performed throughout the study (according to the Schedule of Activities) to monitor the safety of subjects. Potential risks will be managed and minimized by appropriate protocol eligibility criteria, subject management procedures, specific discontinuation criteria, and careful internal safety monitoring.

Subjects who discontinue early from the study will have a post-study visit, so as to collect information on SAEs, and support a complete assessment of key safety events in the intact randomized study population. Specific monitoring algorithms are provided in case of elevations that warrant further follow-up and investigations in subjects experiencing prespecified elevation of these parameters.

The general scientific aspects of this study are in accordance with established FDA and EMA guidelines for the development of weight-control drugs. 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 an agent, given the dynamic nature of the disease. Similarly, given background occurrence of adverse events 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 drug. However, the importance of the placebo group must be balanced with the increased risk that subjects allocated to placebo may not achieve weight loss and the concomitant benefit of glycemic control. In that regard, some subjects may have glycemic levels that are not consistent with current diabetes guidances during their participation in this study. Therefore, all subjects will receive diet and exercise counseling, undergo regular fingerstick glucose monitoring, and have glycemic rescue therapy implemented with progressively lower glucose cutpoints.

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 adverse events of the study, and provide their consent voluntarily will be enrolled.

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 along with a urine pregnancy test at Day 1, 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.

The total blood volume to be collected is 147.0 mL, which is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (American Red Cross).

4.3. Justification for Dose

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 (HM-OXM-101; see Section 2.2, Background). 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 12 weeks of treatment. Twelve weeks is generally sufficient to assess weight loss and any significant safety issues in a Phase 2 study. The upper end of the dose range was selected because drug exposures are highly variable beyond doses of 10 mg weekly (Study 64565111EDI1002). Moreover, 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. The 7.4 and 10 mg doses are expected to produce clinically meaningful weight reduction and are therefore included in the study. The 5-mg dose was included to add a third anchor point, which is needed to evaluate a dose-response relationship as suggested by the dose-response guidance International Conference on Harmonisation (ICH) E4 (which states: *Several dose levels are needed, at least 2 in addition to placebo, but in general, study of more than the minimum number of doses is desirable*).

4.4. End of Study Definition

A subject will be considered to have completed the study if he or she has completed assessments through Week 12 of the treatment phase.

Subjects who prematurely discontinue study drug for any reason before completion of the double-blind treatment phase will continue in the study and will be followed with selected study procedures at the subsequent visit(s) schedule as post-treatment follow-up (starting at the next scheduled visit when study drug was permanently discontinued up to the final Week 12 visit).

The end of study is considered as the last visit/contact for the last subject 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, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

1. Male or female (according to their reproductive organs and functions assigned by chromosomal complement)

2. 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 70 years of age, inclusive

3. BMI ≥35 to ≤50 kg/m^2 at screening

4. Stable weight (ie, change of ≤5% within 12 weeks before screening based on medical or subject reported history)

5. HbA_{1c} of ≥6.5% and ≤9.5% at screening as determined by the central laboratory and meets one of the inclusion criteria below:

    - On diet and exercise alone ≥12 weeks prior to screening
    - On stable dose of single oral AHA or dual-combination oral AHAs for ≥12 weeks prior to screening (AHAs allowed at screening include: metformin, sulphonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs)

6. Subjects are, in the investigator's opinion, well-motivated, capable, and willing to:

   - perform fasting SMBG testing at least 2 times per week
   - learn how to self-inject treatment, as required for this study

7. On Day 1, subjects must have 100% compliance with the open-label placebo run-in medication based on unused prefilled safety injector(s), used empty study drug carton(s), and/or injections recorded in study drug diary during the pretreatment phase.

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol

9. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

10. 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

11. Women 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 and a negative urine pregnancy test on Day 1.

    Note: In the case of an ambiguous urine pregnancy test result, a serum pregnancy test will be performed and randomization will be delayed by a few days in order to obtain the test result. Subject may only be randomized and receive first dose of blinded study medication if the result of the serum pregnancy test is negative.

5.2. Exclusion Criteria

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

Diabetes-related/Metabolic/Endocrine

1. History of obesity with a known secondary cause (eg, Cushing's disease/syndrome)

2. History of Type 1 diabetes mellitus, DKA, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy

3. Fasting C-peptide <0.7 ng/mL at screening as determined by the central laboratory.

4. Fasting fingerstick glucose of ≥270 mg/dL (≥15 mmol/L) on Day 1

   Note: Fasting fingerstick glucose values may be obtained by study-site staff at the study site or by the subject at home on the morning of Day 1. At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Day 1 criterion may return to the study site within 7 days for a one-time repeat fingerstick glucose and continue in the study if the subject's repeat fingerstick glucose meets the criterion.

5. 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

6. History of glucagonoma

7. Screening calcitonin of ≥50 pg/mL (≥50 ng/L), personal history or family history of medullary thyroid cancer, or of MEN2, 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

8. Myocardial infarction, 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

9. Heart failure of New York Heart Association Class II-IV cardiac disease according to the Criteria Committee of the New York Heart Association Classification of Cardiac Disease (Appendix 4)

10. Findings on 12-lead electrocardiogram (ECG) at Week -2 visit that would require urgent diagnostic evaluation or intervention (eg, clinically important arrhythmia or conduction disturbance)

11. History of tachyarrhythmia (eg, atrial flutter, atrial fibrillation, ventricular tachycardia) within 6 months before screening

12. 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 Appendix 6, Method of Blood Pressure and Pulse Rate Measurement)

13. An average of 3 seated pulse rate readings of <50 or >100 bpm

Gastrointestinal

14. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis)

15. History of acute or chronic pancreatitis

16. History of bariatric surgical procedure or a known clinically significant gastric emptying abnormality (eg, severe gastroparesis or gastric outlet obstruction)

Psychiatric-Related

17. History of a clinically significant eating disorder (eg, anorexia nervosa, bulimia, or binge-eating)

18. Any history of major depressive disorder within the last 2 years

19. Any history of other severe psychiatric disorders (eg, schizophrenia, bipolar disorder, etc.)

20. Any lifetime history of suicide attempt

Laboratory

21. Estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula (Levey 2009) at screening (refer to Appendix 9, 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

22. Alanine aminotransferase (ALT) level is >2.0 times the upper limit of normal (ULN) or total bilirubin is >1.5 times 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

23. 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

24. Serum sodium <130 mEq/L (<130 mmol/L) at screening

Other Conditions

25. 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

26. Previous (ie, within 12 weeks from screening visit) or current use of a highly active anti-retroviral therapy

27. 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

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

Medications/Therapies

29. Previous or current participation in a JNJ-64565111 study

30. Known allergies, hypersensitivity, contraindication, or intolerance to the excipients of JNJ-64565111 (ie, citric acid, mannitol, methionine, and polysorbate 20)

31. Known or potential history of intolerance to any GLP-1 receptor agonist (eg, adverse events, lack of efficacy) which, in the opinion of the investigator, makes participation not in the best interest of the subject

32. 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

33. Use of 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 or plans to initiate non-study-related weight-loss treatment during the study

34. Use of medications that may cause weight change (ie, gain or loss), within the 12 weeks before screening or likely to require treatment with such medications during study treatment phase, including but not limited to the following:

    - Injectable AHAs including exenatide, GLP-1 or GLP-1 analogues, and any type of insulin. (**Note**: if a subject temporarily requires insulin treatment due to a transient condition (eg, due to hospitalization, surgery, or other acute illness) for ≤7 days, they are eligible to participate in the study)
    - Antipsychotic drugs
    - Anticonvulsants
    - Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists

35. 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 because of their potential to cause weight change.

36. 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

37. Received an investigational drug (including investigational 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 screening

39. Female subject is pregnant or breastfeeding, planning to become pregnant during the study or follow-up period, 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 member of an employee or the investigator

41. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

NOTE: Investigators should ensure that all study enrollment 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. The required source documentation to support meeting the enrollment criteria are noted in Appendix 2, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5, Prestudy and Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

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

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) 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.

6. STUDY TREATMENT

6.1. Study Drugs Administered

Open-label AHA Background Therapy

Subjects on oral AHA will be required to have been on a stable treatment regimen (ie. same agent and same dose) for at least 12 weeks prior to screening and to remain on such regimen throughout the remainder of the study.

Antihyperglycemic agents allowed at screening and as glycemic rescue medication during study are: metformin, sulphonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs.

Basal insulin is not allowed at screening but can be used as a glycemic rescue medication.

On days of protocol-specified study visits, subjects are to withhold their morning dose of subjects' oral AHA until after the completion of all study visit procedures.

JNJ-64565111/Placebo During Run-in Period

At the Week -2 visit, subjects will be instructed on the use of prefilled 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 once weekly SC injections are eligible to participate in the study (see Section 5.1, Inclusion Criteria). To assess compliance with the dosing regimen, eligible subjects will be dispensed prefilled safety injectors containing 0.5 mL open-label placebo and instructed to perform self-injections once weekly at home during the run-in phase, as well as keep a study drug diary of their injection schedule.

Double-blind JNJ-64565111 or Matching Placebo During Double-Blind Treatment Period

JNJ-64565111 will be supplied as a solution for injection at a concentration of 20 mg/mL. Blinded study drug will be provided in prefilled safety injectors with attached SC needle, prefilled 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. The prefilled 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.

On Day 1, subjects randomly assigned to the double-blind treatment arms will receive a supply of their randomly-assigned study drug 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.

Drug Administration

Subjects will be instructed to administer study drug SC once weekly for the entire duration of the 12-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 days proceed in the next quadrant in a counterclockwise manner.

Injections can be done at any time of day irrespective of meals. However, it is preferable that study drug be injected during the same overall time period of the day on a week-to-week basis.

Study drug should be taken on the same day of the week throughout the study (ie, the regularly scheduled study drug day).

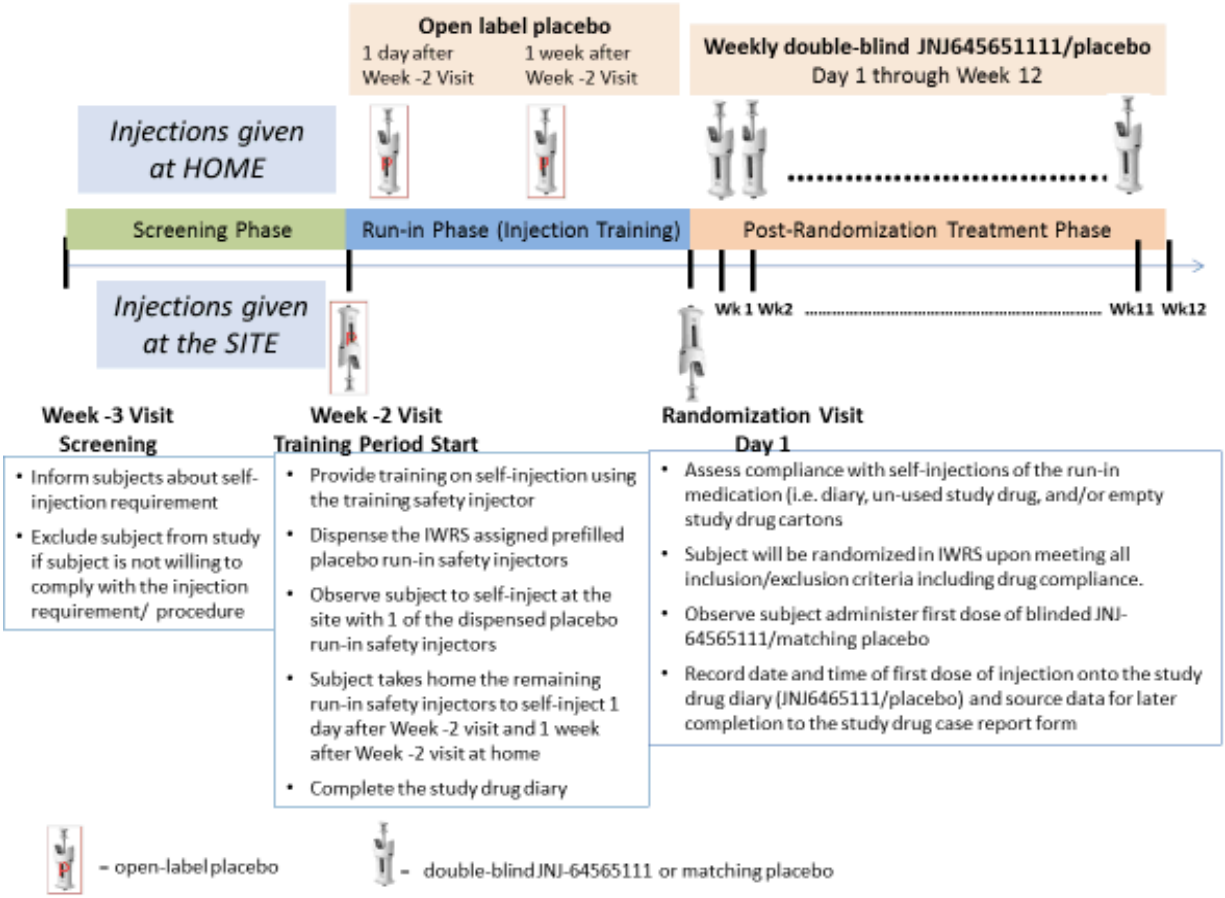
If the day of the once weekly injection coincides with the day of a clinic visit, subjects are NOT to inject JNJ-64565111 or matching placebo before arriving at the clinic. Instead, AFTER all study visit procedures have been completed, subjects may self-administer blinded study drug either at the study site or once they have returned home.

Subjects are to record the date and time of study drug administration on the study drug diary, and should mark a calendar to remind them of when to take the next weekly dose. Subjects will 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 to the time of study-drug dosing. The information will be entered into eCRFs by the site personnel.

Subjects 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 study drug 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.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. Figure 3 is a schematic diagram of the study drug injection schedule.

Figure 3: Schematic Diagram of Drug Injection Schedule



6.2. Preparation/Handling/Storage/Accountability

All study drug should be stored in the refrigerator at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C). Site should keep the study drug cartons until ready to be used, protect them from direct heat and light, and avoid shaking the safety injectors. Study drug can be left out at room temperature up to 8 hours.

Study drug administration should be captured in the source documents and eCRF. JNJ-64565111 will be manufactured and provided under the responsibility of the sponsor.

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 and/or interactive web response system (IWRS) drug accountability web portal. Details on drug accountability will be outlined in the IWRS site user manual. All study drug will be stored and disposed of according to the sponsor's instructions.

Subjects should be instructed to return the following at the drug return visits:

- unused safety injectors
- empty study drug cartons
- study drug diary

Study drug must be handled in strict accordance with the protocol and the study drug 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, and 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 and/or IWRS drug accountability web portal. 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 and/or IWRS drug accountability web portal.

Potentially hazardous materials such as 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 of 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization and Blinding Procedures

On Day 1, subjects will be randomly assigned to 1 of 4 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.

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

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 study drug assignment (ie, study drug serum concentrations, anti-JNJ-64565111 antibodies, study drug preparation/accountability data, study drug allocation, FPG, $HbA1_c$, serum β-hydroxybutyrate, and urine ketones) 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. The investigator may in an emergency determine the identity of the study drug by contacting the IWRS. While the responsibility to break the study drug code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. 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 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.

6.4. Study Drug Compliance

The investigator or designated study-site personnel will maintain a log of all study 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 study drug (based on unused safety injector(s), used empty study drug cartons, and/or study drug diary) should receive counseling on the importance of dosing compliance.

During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instructions to re-educate any subject who is not compliant with taking the study drug.

6.5. Prestudy and Concomitant Therapy

Prestudy 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.

Prestudy therapies administered up to 30 days before first dose of double-blind 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, special diets, exercise regimens) different from the study drug must be recorded in 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 a highly active anti-retroviral therapy
4. GLP-1 agonists and any insulin except basal insulin that serve as rescue AHA use

   Note: if a subject temporarily requires insulin treatment due to a transient condition (eg, due to hospitalization, surgery, or other acute illness) for ≤7 days, they may remain in the study
5. Antipsychotic drugs
6. Anticonvulsants
7. Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists
8. 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.

6.6. Glycemic Rescue Medication

During the 12-week treatment phase, glycemic rescue therapy will be implemented in subjects with FPG values (repeated and confirmed within 7 days) meeting the prespecified criteria provided in Table 3 below. Subjects should be counseled to contact the site if their fasting SMBG consistently (ie, ≥3 days within a week) exceeds 200 mg/dL, and an FPG measurement to determine eligibility for glycemic rescue therapy should be obtained. Subjects should have reinforcement of diet and exercise recommendations before obtaining the repeat FPG value. At the investigator's discretion, based upon recent fasting SMBG values that are consistent with the initial FPG result meeting glycemic rescue criteria, this single FPG (ie, without a repeat FPG value) may be used to demonstrate eligibility for glycemic rescue therapy.

Table 3: Glycemic Rescue Criteria

Time point	Value
After Day 1 through Week 6	FPG >270 mg/dL (>15 mmol/L)
After Week 6 through Week 12	FPG >240 mg/dL (>13.3 mmol/L)

Rescue therapy may include increasing the dose of a current AHA or the initiation of a new AHA. Investigators will manage rescue therapy, including the selection of the specific AHA, its clinically appropriate initial dose and titration regimen (if applicable), the need to switch from one AHA rescue medication to another (eg, poor glycemic response to prior rescue medication), and be consistent with the labeled use within the country of the study site. Metformin, sulphonylureas, TZDs, SGLT-2 inhibitors, DPP-4 inhibitors, and insulin (basal only) are allowed as rescue medication. Both GLP-1 agonists and short-acting or intermediate insulins are not allowed as rescue medications.

Subjects on glycemic rescue therapy for at least 2 weeks at the maximum dose considered appropriate by the investigator, with FPG >180 mg/dL (10.0 mmol/L), must be discontinued from the study drug treatment (see Section 7, Discontinuation from Study Drug and Discontinuation from Study).

6.7. Dose Modification

JNJ-64565111 or matching placebo will not be titrated. Subjects will self-administer the full dose of JNJ-64565111 or matching placebo on Day 1 and will remain on their assigned dosages throughout the treatment phase (ie, until Week 12 or early discontinuation of study drug).

6.8. Study Drug After the End of the Study

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.

7. DISCONTINUATION FROM STUDY DRUG AND DISCONTINUATION FROM STUDY

7.1. Discontinuation from Study Drug

A subject's study drug must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The investigator formally unblinds the subject's treatment allocation
- Subject is persistently in poor compliance with study treatment or procedures
- Subject's eGFR is <45 mL/min/1.73 m^2 (provided by the central laboratory)
  - 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 persistent 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
- 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.

- Liver function test abnormalities occur that meet the criteria for permanent discontinuation of study drug as outlined in Appendix 10, 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 >3 x ULN or characteristic findings on CT/MRI (see Appendix 11, Pancreatitis Monitoring and Withdrawal Criteria)
- The subject becomes pregnant (study drug should be immediately interrupted based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β-hCG)
- Initiation and planned continued use of disallowed therapy (see Section 6.5, Prestudy and Concomitant Therapy)
- Subject is on glycemic rescue therapy, and after at least 2 weeks on the maximum dose considered appropriate by the investigator, FPG is >180 mg/dL (10.0 mmol/L)

- Subject experiences a SAE of biochemically-confirmed (eg, blood pH, serum ß-hydroxybutyrate, anion gap) DKA
- 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).

Subjects who prematurely discontinue study drug prior to Week 12 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 SAE assessment/follow-up and PK and immunogenicity (ie, ADA) collection at least 5 weeks since the last dose of study drug.

Subjects that discontinue study drug early will continue in the study (off treatment) and will be assessed at the subsequent visit(s) as described in the Schedule of Activities schedule, starting at the next scheduled visit from when study drug was permanently discontinued up to the final Week 12 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

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, MACEs (ie, CV death, nonfatal MI and nonfatal stroke), acute pancreatitis, and AEs of thyroid neoplasm. Details regarding discussions via telephone, email, or other methods of contact should be properly documented on subject's source record and/or 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.

7.2. Discontinuation from the Study

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

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

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.

7.2.1. 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 study should only be documented in the eCRF after a discussion between the investigator and the appropriate sponsor representative (eg, study responsible physician).

7.2.2. Withdrawal from the Use of Research Samples

Withdrawal from the Use of Archive Samples in Future Research

The subject may withdraw consent for use of archive samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 2, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. 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 should be documented.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

Scheduled study visits should generally occur within a 3-day window (ie, ±4 days) around the protocol-specified visit schedule (as provided in the Schedule of Activities). 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.

The maximum blood volume (for blood collections shown in the Schedule of Activities) that would be collected if a subject were to complete the SAE follow-up visit after the Week 12/EOT visit would be approximately 147.0 mL. See Table 4 for details. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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 lab assessments will be recorded in the source documentation (eg, lab requisition form).

Table 4: Maximum Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per subject	Total Volume of Blood (mL)[a]
Hematology	1.0	3	3.0
HbA_{1c}	2.0	5	10.0
Serum chemistry	2.5	5	12.5
Calcitonin	1.0	3	3.0
Serum β-hydroxybutyrate	1.0	4	4.0
Fasting insulin	2.0	2	4.0
Fasting C-peptide	1.0	3	3.0
FPG	2.0	5	10.0
Fasting lipid panel	3.5	3	10.5
Serum β-hCG pregnancy tests	1.5	2	3.0
FSH	1.5	1	1.5
Pharmacokinetic (PK) trough and immunogenicity samples	5.0	5	25.0
PK non-trough	3.5	1	3.5
Plasma, serum archive samples	27	2	54
Approximate Total			147.0

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

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form.

Refer to the Schedule of Activities 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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Glucose meter and glucose testing strips
- Recruitment and retention tools
- IWRS Manual and worksheets
- Template ICFs
- eCRF completion guidelines
- Materials to promote healthy dietary and exercise habits
- Study drug diary (ie, JNJ64565111/Placebo diary)

- Blood sugar diary (including SMBG results, hypoglycemia events, and concomitant medications)
- IWQOL-Lite questionnaire
- 7-day ERCQ diary
- PROMIS SF 10a questionnaire
- PGIS questionnaire
- PGIC questionnaire
- Survey on Subject Satisfaction with Self-injection (English-speaking subjects)
- 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
- PRO Completion Guide

8.1. Efficacy Assessments

Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage change in body weight from baseline to Week 12 between JNJ-64565111 compared with placebo.

Secondary and Exploratory Efficacy Endpoints

The secondary measures of efficacy at Week 12 include proportion of subjects with ≥5% weight loss from baseline, and the absolute change in body weight from baseline.

Exploratory efficacy endpoints at Week 12 include proportion of subjects with ≥10% weight loss from baseline, change from baseline in BMI, waist circumference, HbA_{1c}, FPG, fasting insulin, fasting C-peptide, HOMA-B, HOMA-IR, fasting lipids (ie, total cholesterol, LDL-C, HDL-C, triglycerides), SBP, DBP, pulse rate, pulse-pressure product, PK exposure, and PROs (ie, changes in IWQOL-Lite, PROMIS SF 10a, ERCQ).

Patient-reported Outcomes

Janssen is developing a novel PRO instrument 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 a previously developed questionnaire will be included in this study. Some questionnaires will be completed during scheduled site visits (IWQOL-Lite, PROMIS SF 10a, PGIS, PGIC) while another will be completed at home by the subject (ERCQ). It is therefore important for sites to be familiar with the Schedule of Activities to ensure subjects complete the PROs at the correct setting and visit (see Appendix 13). 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.

Whenever possible, all site-visit-based PRO assessments (IWQOL-Lite, PROMIS SF 10a, PGIS, PGIC) should be completed before any tests, procedures, or discussion of AEs or the subject's medical condition. The home-based PRO assessment (ERCQ) should be completed daily, preferably in the evening, and, whenever possible, in the same setting for 7 consecutive days.

All PRO assessments will be done in English-speaking and Spanish-speaking subjects provided that a suitable Spanish translation of the materials are available, otherwise, the PRO assessments will only be administered to English-speaking subjects.

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 -2 and 12/EOT visit. A sample of the IWQOL-Lite and instructions for completion are provided in the PRO Completion Guide.

Eating-related Concepts Questionnaire (ERCQ)

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

At the Week -2 visit, subjects 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 the Week 6 visit, another ERCQ diary will be provided to the subjects to start completing at around Week 11. The site should contact subjects at Week 10, preferably by telephone, to remind the completion of this ERCQ diary 7 consecutive days starting at Week 11 up to the day prior to their scheduled Week 12 visit. The completed final ERCQ diary should be returned by the subjects and collected by the site at the Week 12 visit. For subjects who discontinue early from study drug, no ERCQ diary completion is required at the EOT visit. A sample of the ERCQ and instructions for completion are provided in the PRO Completion Guide.

PROMIS Physical Function Short Form 10a (PROMIS SF 10a)

The Patient-Reported Outcomes Measurement Information System (PROMIS®) 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).

The PROMIS SF 10a will be administered at Week -2, baseline Day 1, and Week 12/EOT visit. A sample of the PROMIS SF 10a and instructions for completion are provided in the PRO Completion Guide.

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 10a in this population of severely obese subjects with T2DM. 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 with before starting the study.

The PGIS will be administered at Week -2 and Week 12/EOT visit and PGIC at Week 12/EOT visit only. Samples of the PGIS and PGIC and instructions for completion are provided in the PRO Completion Guide.

8.2. Safety Assessments

Safety evaluations will include the monitoring of AEs (including protocol-specified AEs of interest), vital sign measurements, clinical laboratory tests (including serum chemistry, calcitonin, lipase, amylase, hematology, and urinalysis), physical examination including complete skin examination, serum/urine pregnancy testing, ECG, SMBG, assessment of hypoglycemia episodes, and review of concomitant medications.

At Week -2, subjects will be provided with and instructed on the use of a home blood glucose meter that will measure their fasting SMBG (to be done at least twice weekly). Subjects will be counseled on the signs/symptoms and how to manage an episode of hypoglycemia (see

Appendix 8, Hypoglycemia: Definitions, Symptoms, and Treatment). In addition, subjects should be counseled to contact the site if their fasting SMBG consistently (ie, ≥3 days within a week) exceeds 200 mg/dL, and an FPG measurement to determine eligibility for glycemic rescue therapy should be obtained (see Section 6.6, Glycemic Rescue Medication).

Investigators will remind subjects to contact the investigational sites in the presence of signs/symptoms that may be consistent with acute pancreatitis (see Appendix 11, Pancreatitis Monitoring and Withdrawal Criteria), 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, as well as DKA. 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 Appendix 1, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) 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 7.1, Discontinuation from Study Drug).

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) and any other clinical data, 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 7.1, Discontinuation from Study Drug).

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

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 will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events, and Appendix 1, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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 the study/early withdrawal 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 Schedule of Activities:

8.2.1. Physical Examination

Physical examinations will include a full review of body systems including a complete skin examination. Physical examination abnormalities noted after the baseline assessment will be collected if considered an adverse event by the investigator (recorded on adverse event eCRF). In addition to the physical examination required at the screening visit and EOT visit, investigators should use their clinical judgment whether additional physical examinations (either full of focused) are needed (eg, subject reporting injection site reaction, flank pain, pedal edema, etc.).

8.2.2. Vital Signs

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 Schedule of Activities and in Appendix 6, Method of Blood Pressure and Heart 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.

8.2.3. 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.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology, and urine samples for urinalysis will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event eCRF if applicable.

Subjects will be monitored for safety laboratory analytes as described in Appendix 9, Clinical Laboratory Tests.

Subjects with elevations in ALT (≥3 × ULN), in lipase/amylase (≥2 × ULN) or in calcitonin (≥10 pg/mL [≥10 ng/L]) will be monitored and managed using the algorithms provided in Appendix 10, Algorithm for Monitoring Abnormal Liver Function Tests, Appendix 11, Pancreatitis Monitoring and Withdrawal Criteria, and Appendix 12, Guidelines for Calcitonin Monitoring.

In the current study, serum β-hydroxybutyrate will be assessed by the central lab as a marker of target engagement as mild elevations of serum β-hydroxybutyrate were generally observed in the Phase 1 studies (see Section 2.3, Benefit/Risk Assessment). To avoid the potential unblinding of subject to treatment assignment, both serum β-hydroxybutyrate and urinary ketones will remain masked to investigators and sponsor.

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.

8.3. Adverse Events and Serious Adverse Events

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.

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 of AEs.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 1, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Collection of Protocol-Specified Adverse Events of Interest

For any adverse event considered to be one of the following protocol-specified adverse events of interest, and for all deaths, investigators may be asked to provide more detailed information with the source documents or completing the applicable supplemental forms 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:

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

See Appendix 11, Pancreatitis Monitoring and Withdrawal Criteria, for details of how to monitor and document pancreatic adverse events.

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 Appendix 12, Guidelines for Calcitonin Monitoring, for details of how to monitor and document thyroid neoplasm.

Collection of Information on Possible Hypoglycemic Episodes

Subjects will be asked to collect fingerstick glucose determinations at the time of possible hypoglycemic episodes, and to document information on these events, including the fingerstick glucose results, in the blood sugar diary. This diary will be reviewed by study-site personnel at each scheduled visit (see Appendix 8, Hypoglycemia: Definitions, Symptoms and Treatment). Information on possible hypoglycemic episodes will be collected on a separate hypoglycemia eCRF, and hypoglycemic episodes that are considered by the investigator to be adverse events of hypoglycemia should also be recorded on the adverse event eCRF.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events 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 after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 eCRF, 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 an SAE should be transmitted electronically or by facsimile (fax).

8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 1, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events 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/Institutional Review Board (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.

8.3.4. 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, or 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.

8.4. Treatment of Overdose

For this study, more than 3 doses/injections of JNJ-64565111within a 7-day time period will be considered an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the subject for AE/SAE and laboratory abnormalities.

No antidote to JNJ-64565111 is available. The sponsor does not recommend specific intervention for an overdose, but rather appropriate symptomatic medical treatment should be given according to the clinical condition.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of JNJ-64565111. Serum collected for PK 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.

Evaluations

Refer to the Schedule of Activities 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.

Venous blood samples will be collected from all subjects according to the Schedule of Activities for determination of serum trough concentrations of JNJ-64565111 to assess attainment of steady-state concentrations. In addition, a non-trough (peak) sample on Day 4 will be collected from all subjects, as well as a post-treatment sample at 16 weeks from 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 non-trough PK sampling time point was prospectively optimized for population-based PK analyses. In addition to the trough samples and a post-treatment sample in all subjects, all subjects will have 1 additional visit (Day 4±1-day sampling window) to collect a non-trough PK sample.

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.

Pharmacokinetic 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.

Parameters

Serum concentrations at each time point of measurement will be evaluated by descriptive statistics, including arithmetic mean, geometric mean, standard deviation, coefficient of variation, geometric coefficient of variation, minimum, maximum, and median.

8.6. Pharmacodynamics

Pharmacodynamics are part of efficacy, see Section 8.1, Efficacy Assessments.

8.7. Genetics

Pharmacogenomics/Genetics are not evaluated in this study.

8.8. Archive Samples for Exploratory Biomarker Research

Archived samples may be used for future analysis of biomarkers related to the safety and/or efficacy of JNJ-64565111, and/or the study of T2DM, obesity, and its complications.

8.9. Health Economics/Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10. Further Assessments

8.10.1. Immunogenicity Assessments

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 Schedule of Activities. Additionally, serum samples should also be collected at the final visit from subjects who are discontinued from treatment.

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.

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

A survey designed to assess subject satisfaction with the experience of self-administering study drug will be given to English-speaking subjects at Week 6.

9. STATISTICAL CONSIDERATIONS

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.

9.1. Statistical Hypotheses

The goal of the primary efficacy analysis is to determine if there is treatment difference in the percentage reduction in body weight from baseline between JNJ-64565111 treatment groups and the placebo group at Week 12. The null hypothesis is that there is no difference between the treatment groups in the percentage reduction in body weight. The alternative hypothesis is that there is a greater percentage reduction in body weight in the JNJ-64565111 treatment groups compared with placebo group.

9.2. Sample Size Determination

A total of 188 subjects will be randomly assigned in this study with 47 subjects per group allocated to each of the 4 treatment groups. Sample size was determined based on assessing the primary hypothesis that treatment with JNJ-64565111 at 1 or more dose levels for 12 weeks leads to greater percentage reduction in body weight compared with placebo.

Assuming a common SD of 4% with respect to percent change in body weight at Week 12 and a 2-sided type I error rate of 0.05, it is estimated that a sample size of 47 randomly assigned subjects per group will have approximately 90% power to detect a treatment difference of 2.7%.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 5: Subject Population Definitions

Population	Description
Enrolled	All subjects who sign the ICF
ITT analysis set	all subjects who are randomly assigned to a treatment group and have a baseline measurement of body weight
mITT analysis set	all ITT subjects who have at least 1 post-baseline measurement of body weight within 7 days following a dose of study drug and before initiation of any rescue therapy
Completers' analysis set	of all mITT subjects who have completed 12 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 12 visit) and without initiation of glycemic rescue therapy
Safety analysis set	all randomized subjects who have received at least one dose of study drug

Key: eCRF=electronic case report form; ICF=informed consent form; ITT=intent-to-treat; mITT=modified intent-to-treat.

The primary efficacy analysis, to demonstrate the superiority of JNJ-64565111 compared with placebo on percentage reduction in body weight from baseline to Week 12, as well as all secondary efficacy analyses, will be based on the modified intent-to-treat (mITT) analysis set and will include only those measurements taken up to and including the last dose of study drug plus 7 days and prior to initiation of any glycemic rescue therapy. A secondary analysis of the primary and secondary efficacy endpoints will be based on the intent-to-treat (ITT) analysis set. 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.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

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

Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage change in body weight between JNJ-64565111 and placebo from baseline to Week 12.

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 12 while on treatment (up to the last dose of study drug plus 7 days) and prior to rescue medication. The analysis model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the 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 12 based on this model.

A secondary analysis of the primary endpoint will be based on the ITT analysis set and will employ pattern mixture models using multiple imputation methods. This analysis will use all observed data, including the measurements off treatment. Responses for subjects who discontinued from the study earlier than Week 12 will be imputed based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. The imputation will be done within randomized treatment groups. 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 12. 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 Multiple Comparison Procedure – Modeling approach (Bornkamp 2009; Pinheiro 2014) will be performed to explore the dose-response relationship.

Secondary Efficacy Endpoints

Secondary efficacy analyses at Week 12 will include the absolute change in body weight from baseline and the proportion of subjects with ≥5% weight loss.

The absolute change in body weight from baseline at Week 12 will be analyzed with an MMRM model similar to the primary efficacy endpoint based on the mITT analysis set.

The proportion of subjects with ≥5% weight loss will be analyzed longitudinally using a generalized linear mixed model based on the mITT analysis set. The analysis will use the observed data through Week 12 while on treatment (up to the last dose of study drug plus 7 days) and prior to rescue medication. The model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous 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 12 based on this model will be provided.

A secondary analysis of the secondary endpoints will be based on the ITT analysis set and will employ pattern mixture models using multiple imputation methods based on information from retrieved dropouts as described above. For the proportion of subjects with ≥5% weight loss, 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 the primary endpoint and secondary endpoints. The Hochberg approach will be used to adjust the multiplicity of the comparisons of each of the JNJ-64565111 doses versus placebo for each endpoint.

Exploratory Endpoints

The continuous exploratory efficacy endpoints will be analyzed using a MMRM model similar to the model used to analyze the primary efficacy endpoint based on the mITT analysis set. The categorical exploratory efficacy endpoints will be analyzed using a generalized linear mixed model similar to the model used to analyze the proportion of subjects with ≥5% weight loss.

9.4.2. Safety Analyses

The evaluation of safety will be based on the incidence of adverse events and hypoglycemia episodes, and changes in clinical laboratory test results and vital sign results (blood pressure, pulse rate). The safety analyses will be based on the safety analysis set including all data, regardless of the initiation of glycemic rescue therapy (ie, including data after initiation of rescue therapy). Additional analysis of hypoglycemia will be performed based on the data prior the initiation of glycemic rescue therapy only. Summaries of adverse events, clinical laboratory test results, and vital sign results will be provided by treatment group. There will be no imputation of missing values for clinical safety laboratory test results, and vital sign measurements.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study drug due to an adverse event, or who experience a severe or a serious adverse event.

For each adverse event, 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 treatment-emergent adverse events (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.

Hypoglycemic events will be classified as severe, documented symptomatic, probable symptomatic and asymptomatic. The primary hypoglycemic analysis of interest will be all documented hypoglycemic events regardless of the presence of symptoms (ie, documented symptomatic and asymptomatic hypoglycemia) plus all severe hypoglycemic events. For each type of hypoglycemia, the percentage of subjects with at least one event will be summarized by treatment group. The differences in percentage (JNJ-64565111 versus placebo) and their 2-sided 95% confidence intervals will be estimated.

Hypoglycemic events are collected on a separate eCRF and also collected on the Adverse Event eCRF (for all such events considered as adverse events by the investigator). The primary analysis of hypoglycemia will be based upon data from the hypoglycemia eCRF (and not from the adverse event database). No reconciliation of hypoglycemia data from the Adverse Event eCRF and the hypoglycemic eCRF will be performed (except to assure that all adverse events of hypoglycemia are also recorded on the hypoglycemia eCRF).

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 adverse events for which additional information is collected from the investigators (refer to Section 8.2, Safety Assessments), and on other adverse events.

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.

Resting Vital Signs (Pulse, Blood Pressure)

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

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

9.4.3. Other Analyses

Pharmacokinetic Analyses

If feasible, population PK analysis of serum concentration-time and exposure-response 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, lack of compliance with 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), arithmetic mean, geometric mean, SD, percent coefficient of variation, percent geometric coefficient of variation, median, minimum, and maximum will be calculated for serum concentrations for JNJ-64565111 at each time point.

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.

9.5. Interim Analysis

No interim analyses are planned.

9.5.1. Internal Data Monitoring Committee (DMC)

The study team will perform ongoing blinded monitoring of the study safety data. If during the review the study team notes any possible safety signal(s), the study team may request an internal DMC to review unblinded study data.

The internal DMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The internal DMC responsibilities, authorities, and procedures will be documented in its charter. After the review, the internal DMC will make recommendations regarding the continuation of the study or any changes in study conduct. The details will be provided in a separate internal DMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 study drug. 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 adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, 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 adverse event 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 adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

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 below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the study drug.

Doubtful

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

Possible

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

Probable

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

Very Likely

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

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).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting 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 serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported, according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the subject should 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

Serious Adverse Events

All serious adverse events 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 serious adverse event. 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 serious adverse event, 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 serious adverse event.

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.

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.

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 serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

If the product quality issue relates to the device (ie, 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.

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.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

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.

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) involve 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.

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.

Required Prestudy 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 principal investigator
- 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 principal investigator, 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

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 adverse events 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).

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 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1, Study-Specific Ethical Design Considerations.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

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. 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. It also denotes that the subject 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 physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

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.

DATA PROTECTION

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 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.

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.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study 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 to 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 (refer to Section 7.2.2, Withdrawal from the Use of Research Samples).

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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 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 for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

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 (ICMJE) 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 substudy 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 18 months after the study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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.

DATA QUALITY ASSURANCE

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.

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 the 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.

All participative measurements (eg, questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

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.

SOURCE DOCUMENTS

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 adverse events and follow-up of adverse events; concomitant medication; study 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 eSource 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 eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

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.

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.

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.

STUDY AND SITE CLOSURE

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

10.3. Appendix 3: Abbreviations and Trademarks

5-HT_{2C}	5-hydroxytryptamine type 2C receptor
β-hCG	serum β-human chorionic gonadotropin
ADA	anti-drug antibodies
AE	adverse event
AHA	antihyperglycemic agent
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
C_{max}	maximum 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-4	dipeptidyl peptidase-4
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
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	GLP-1 receptor
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
MACE	major adverse cardiac event
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
NOAEL	No Observed Adverse Effect Level
OXM	oxyntomodulin
PD	pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression Status
PI	Principal Investigator
PK	pharmacokinetics
PQC	product quality complaint
PRO	patient-reported outcome(s)
PROMIS SF 10a	PROMIS physical function Short Form 10a
QTcR	Rautaharju corrected QT interval
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous, subcutaneously
SD	standard deviation
SGLT-2	sodium-glucose cotransporter 2
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE(s)	treatment-emergent adverse event(s)
$t_{½}$	terminal half-life
T_{max}	time to maximum concentration
TZD	thiazolidinedione
ULN	upper limit of normal
US	United States
WHO	World Health Organization

10.4. Appendix 4: New York Heart Association Classification of Cardiac Disease

The following table represents the New York Heart Association 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.

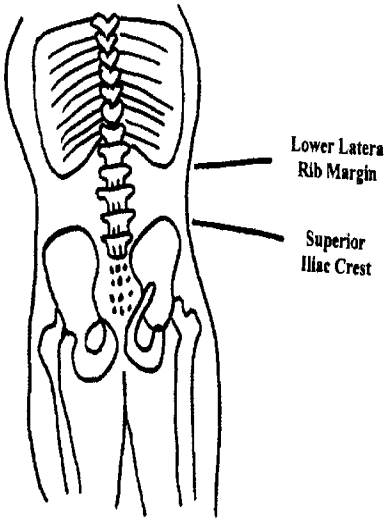
Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

10.5. Appendix 5: 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

10.6. Appendix 6: 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 mm Hg above the point at which the radial pulse disappears. Deflate the mercury column at 2 to 3 mm Hg 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.

At screening visit, blood pressure should be measured in both arms (in triplicate as noted above). Record the triplicate readings from the arm with the higher blood pressure in the screening vital sign eCRF page

and note which arm in the source documents for future reference. The arm with the higher blood pressure should be used for all subsequent blood pressure measurements during the study to reduce any potential inter-arm variability.

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).

10.7. Appendix 7: 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.

10.8. Appendix 8: Hypoglycemia: Definitions, Symptoms, and Treatment

Hypoglycemia is defined and classified as follows:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose (PG) concentration ≤70 mg/dL (3.9 mmol/L)

Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG concentration ≤70 mg/dL (3.9 mmol/L)

Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination.

Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer a carbohydrate, glucagon, or other resuscitative actions. A subject is considered to "require assistance" if he/she is unable to help himself/herself. An act of kindness to assist a subject when it is not necessary does not qualify as "requiring assistance". These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.

The classification of hypoglycemic episodes will determine how the event is captured in the eCRF.

Symptoms

Subjects will receive counseling regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia and other specific details will be captured in the blood sugar diary, which will be returned to the study site for review by study-site personnel at each visit. The following list of symptoms is not meant to be exhaustive but represents the more common symptoms associated with hypoglycemia:

- Seizure
- Loss of consciousness
- Headache
- Tremor
- Hunger
- Sweating
- Nervousness
- Palpitations
- Light headedness
- Blurred vision
- Disorientation
- Dizziness
- Feeling faint

Treatment

The treatment of hypoglycemia requires the ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Therefore, glucose (15 to 20 g) is the preferred treatment for hypoglycemia. Although pure glucose may be the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose and may be used. Adding protein to a carbohydrate does not affect the glycemic response and does not prevent subsequent hypoglycemia. However, adding fat may retard and then prolong the acute hypoglycemic response. Treatment effects should be apparent within 15 minutes although the effects may only be temporary. Therefore, PG should be retested in approximately 15 minutes, as additional treatment may be necessary.

10.9. Appendix 9: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Blood samples for serum chemistry and hematology, and urine samples for urinalysis will be collected at timepoints specified in the Schedule of Activities. 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
  -pancreatic amylase
  -lipase
  -calcium
  -phosphate
  -albumin
  -total protein

- Serum ß-hydroxybutyrate
- Serum calcitonin
- Fasting insulin*
- Fasting C-peptide*
- 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 12/EOT visits along with a urine pregnancy test at Day 1. 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

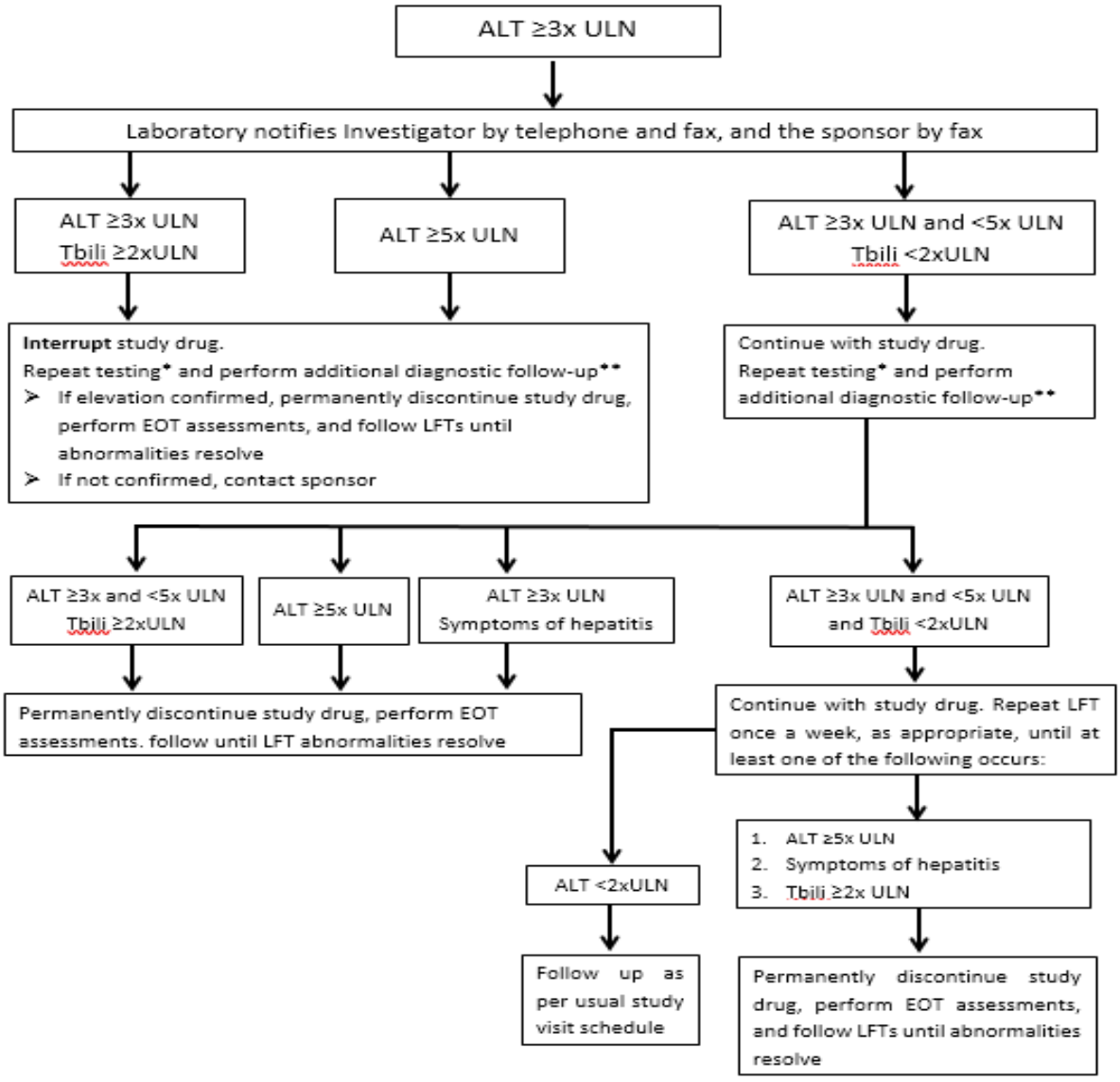
CKD-EPI Formula (for S_{cr} expressed in μmol/L)

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

$\kappa = 61.9$ 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.

10.10. Appendix 10: 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, alanine aminotransferase, aspartate aminotransferase, 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 (≥5 x ULN) or total bilirubin (≥2 x ULN) 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-hepatitis A virus, HBsAg, anti-HBs, anti-HB core, anti-hepatitis C virus (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.

10.11. Appendix 11: 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 ≥2 x ULN, or
- Serum lipase ≥2 x 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 >3 x 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).

10.12. Appendix 12: 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 calcitonin levels 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] 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 (eg, calcitonin levels return to the normal range by ~10 days after stopping proton pump inhibitors).

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 considered to be reported as an AE per investigator's assessment if no previously documented elevation of calcitonin prior to study entry.

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.

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 medullary thyroid carcinoma or multiple endocrine neoplasia type 2 should be evoked and a rearranged during transfection (RET) proto-oncogene analysis should be undertaken.

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

10.13. Appendix 13: 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 Time & Events schedule to ensure subjects complete the PROs at the correct setting and visit. Please refer to the PRO Completion Guide for further information.

Site Responsibilities (General)

For this study, we expect that it will take approximately 15 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 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 diary 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.

10.14. Appendix 14: Protocol Amendment History

This is an original protocol.

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INVESTIGATOR AGREEMENT

JNJ-64565111
Clinical Protocol 64565111OBE2002 – 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): Nicholas Di Prospero, MD, PhD

Institution: Janssen Research & Development

Signature: [redacted] Date: 23 AUG 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