Janssen Research & Development

Statistical Analysis Plan

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

Protocol 64565111OBE2001; Phase 2b
Amendment 1

JNJ-64565111 (LAPS-GLP1/Glucagon dual receptor agonist)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

SECTION(S)	CHANGE and RATIONALE
Global Change	"Pulse Pressure Product" and "Rate Pressure Product" were used interchangeably; the term "Rate Pressure Product" will be used going forward.
1.1, 1.3, 5.4.1	Reworded the objectives and hypotheses to enhance clarity of phrasing (eg, "absolute change from baseline in body weight" from "absolute change in body weight from baseline"
2.1	Visit windows now include post-Week 26 to account for subjects brought back for visits after Week 26 to reduce subjects who were lost to follow-up.
2.3.2	Refined mITT Analysis Set definition to include subjects taking at least one dose of study medication
2.3.2	Clarify that the Completers' Analysis Set is defined by the Treatment Disposition eCRF status
2.3.2	Added ABPM analysis set
4.1	Demographics tables will be generated for 5 analysis sets: ITT, mITT, Safety, PK, and Completers. Within each analysis set, the number of subjects stratified within the ABPM/non-ABPM groups will be provided.
4.2	Screen failures will not be summarized. Protocol deviations will be listed that may include deviations related to medication dispensed.
4.3	Treatment compliance formula was refined to only account for period of time between first and last dose; non-compliance is not counted after the last dose.
4.4	For the purpose of summarizing exposure, Treatment Duration does not take drug interruptions into account. Steps for imputing missing treatment end dates were refined.
4.5	Protocol deviations, as identified by the Study Team, will be listed but not summarized.
5.0, 5.2.3	"Data collected after the last dose plus 7 days" changed to "Data collected after the last dose plus 2 days for liraglutide subjects and 14 days for JNJ64565111 and placebo subjects will be excluded from the mITT analysis." This changed is based on what is known about PK.
5.1	Expanded details related to multiple testing procedures to include the comparison of liraglutide and placebo.
5.1.2, 5.4.2	SBP/pulse and DBP/pulse are not considered endpoints as part of the ABPM analysis
5.2.3	Subgroup and lower-level terms included in model evaluating treatment*subgroup interaction.
5.2.3, 5.4.2	For endpoints with only one post-baseline visit, an ANCOVA model will be used with treatment as a fixed factor and baseline as a covariate.
5.2.3	Change "Sensitivity Analysis" to "Supportive Analysis"
5.2.3, 5.3.2	Allow for copy control method to be used if there are not enough retrieved drop-outs to impute missing data as originally intended.
5.3.2	Clarify that nominal p-values will be provided.
5.3.2	The analysis of categorical endpoints will be performed using logistic regression given the challenges of running a longitudinal categorical analysis in which few subjects at the early time points are considered responders.
5.4.2	Add shift table for obesity class
5.4.2	The endpoint for ABPM is last on-treatment measurement, even if it is not within the Week 26 window.
6	Reference to Section 2.3.4 should be 2.3.3.
6.1	Mild and Moderate AEs will not be pooled for the purpose of summarizing AEs by severity.
6.2, 6.3	References to Attachments 4 and 5 correctly renumbered Attachments 1 and 2, respectively.
6.2	Shift tables for laboratory values will not be generated.
6.2	"Markedly abnormal" laboratory values are not defined.
6.3	Physical examination data will not be listed.
7.1	The details under which measurements should be excluded from the PK analysis are provided.
ATCH 2	Added PDLCs for calcitonin, amylase and lipase
ATCH 2	Beta-Hydroxybutyrate above 208.22 mg/L will be flagged as PDLC.
ATCH 3	Refer to excel files; reference in ERIS.

ABBREVIATIONS

β-hCG	Serum β-human chorionic gonadotropin
ABPM	Ambulatory blood pressure monitoring
ACTT	Anticipations of Clinical Trial Treatment
ADA	anti-drug antibody
AE(s)	Adverse event(s)
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CPK	Creatinine phosphokinase
CT	computed tomography
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF(s)	Electronic case report form(s)
eGFR	Estimated glomerular filtration rate
EOT	End-of-treatment
ERCQ	Eating-related Concept Questionnaire
EW	Early withdrawal
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1R	GLP-1 receptor
HbA_{1c}	Hemoglobin A_{1c}
HDL-C	High-density lipoprotein cholesterol
HOMA-B	Homeostasis Model Assessment for B cell function
HOMA-IR	Homeostasis Model Assessment of insulin resistance
IA	Interim analysis
ITT	Intent-to-treat
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
IWRS	Interactive web response system
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mmHg	Millimeters mercury
MMRM	Mixed model for repeated measures
PAM	Patient Activation Measure
PDLC	Pre-defined limits of change
PGIC	Patient Global Impression of Change
PGIS	PGIS Patient Global Impression Status
PK	Pharmacokinetics
PRO	Patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS SF 8b	PROMIS physical function Short Form 8b
RPP	Rate pressure product
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous, subcutaneously
SD	Standard deviation
SI	International System of Units
SMQ	Standardised MedDRA Query
STEP	Safety, Tolerability, and Efficacy Preview
TEAE(s)	Treatment-emergent adverse event(s)
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) contains the definitions of analysis sets, key derived variables, and statistical methods for the analyses of efficacy and safety data from study JNJ-64565111OBE2001. This SAP is based on Clinical Protocol JNJ-64565111OBE2001 dated 23 August 2018. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures and listings) are provided in a separate document entitled Data Presentation Specifications (DPS). A separate Data Monitoring Committee (DMC) SAP will describe the statistical methods used for the Interim Analysis (IA).

This SAP includes the analyses of the self-administered patient-reported outcome (PRO) measures presented in the clinical study report. A separate SAP contains the statistical methods for the Anticipations of Clinical Trial Treatment (ACTT) and Safety, Tolerability, and Efficacy Preview (STEP) interviews collected in this study.

1.1. Trial Objectives

Primary Objectives

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

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

Secondary Objectives

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

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

Exploratory Objectives

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

- the change from baseline in body mass index (BMI)
- the change from baseline in waist circumference
- the change from baseline in fasting lipids (total cholesterol, LDL-C, HDL-C, triglycerides)
- the change from baseline in fasting plasma glucose (FPG)
- the change from baseline in fasting insulin from baseline
- the change from baseline in fasting C-peptide from baseline

- the changes from baseline in Homeostasis Model Assessment for B cell function (HOMA-B) and HOMA-insulin resistance (IR)
- the change from baseline in systolic blood pressure (SBP)
- the change from baseline in diastolic blood pressure (DBP)
- the change from baseline in pulse rate
- the change from baseline in pulse-pressure product
- in a subset of subjects participating in the 24-hour ABPM assessment, the changes from baseline in 24-hour SBP, DBP, pulse rate, and pulse-pressure product
- Pharmacokinetic (PK) exposure
- the change from baseline in scores on the Impact of Weight on Quality of Life-Lite (IWQOL-Lite),[2,3] single item Ease of Weight Management, and the Patient Activation Measure (PAM)
- in English-speaking subjects in selected countries only, the change from baseline in scores on the eating-related concept question (ERCQ) and the PROMIS physical function short form 8b (PROMIS SF 8b) (Note: the Patient Global Impression Status [PGIS] and Patient Global Impression of Change [PGIC] will be used to calculate responder definitions for these new instruments only and are not exploratory objectives).
- in English-speaking subjects in selected countries only, describe pre-trial goals and expectations as well as post-trial experiences qualitatively using the Anticipations of Clinical Trial Treatment (ACTT) Pre-trial interviews and a modified Safety, Tolerability, and Efficacy Preview (STEP) exit interview

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

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

1.2. Trial Design

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

Subjects meeting all eligibility criteria will enter a 2-week run-in phase, which is to occur approximately 1 week after the screening visit and is designed to train the subject on SC self-injection and to establish the subject's ability to comply with the protocol-specified requirements. On Day 1, approximately 440 subjects who continue to meet eligibility criteria will be randomly assigned in a 1:1:2:2:2 ratio to blinded treatment with placebo, JNJ-64565111 (5.0, 7.4, or 10.0 mg) or open-label liraglutide, stratified by ABPM sub-study participation (yes or no), and then will enter a 26-week treatment phase. Post-randomization visits will be conducted at Weeks 5, 10, 15, 20, 26/end-of-treatment (EOT) visit and 4-week SAE follow-up

after Week 26/EOT visit. A subset of subjects in the ABPM sub-study will have 2 additional visits (ie, Pre-Day 1 and Pre-Week 26). A subset of subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample. All subjects will be contacted preferably by telephone to reinforce the adherence to diet and exercise, study drug dosing reminder, assessment of subjects' status, and compliance with the protocol procedures (eg, diary completion reminder) at Week 2. Study-site staff is encouraged to contact subjects (preferably by telephone) to do the same at some time in between Week 5, 10, 15, 20, and 26 visits. Subjects in the open-label liraglutide treatment group will also be contacted preferably by telephone at Weeks 1, 3, and 4 to remind about the dosing titration (ie, to increase their dose of liraglutide by an 0.6 mg dose increment weekly).

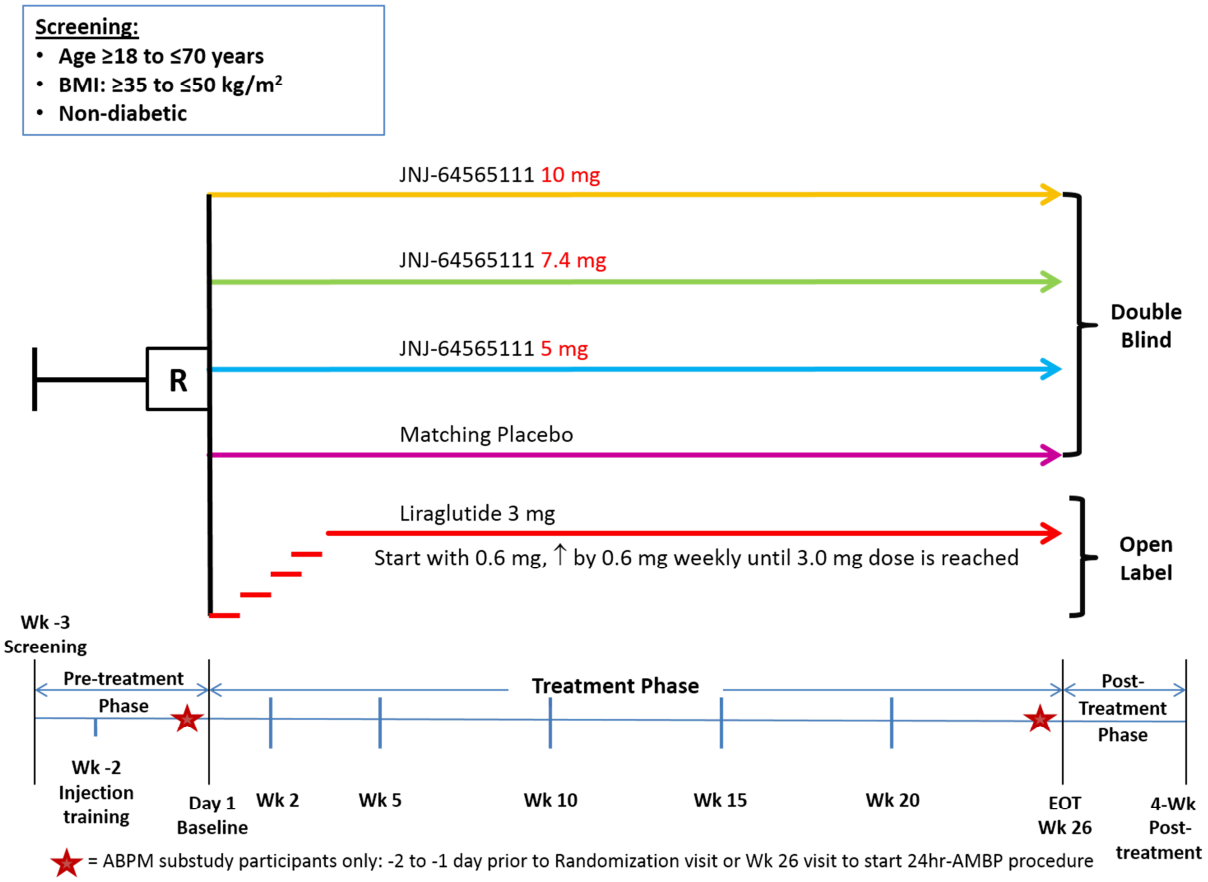
Subjects who withdraw from the study will not be replaced.

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

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

A diagram of the study design is provided in Figure 1.2.1.

Figure 1.2.1: Schematic Overview of the Study



1.3. Statistical Hypotheses for Trial Objectives

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

Primary:

- percentage reduction from baseline in body weight

Secondary:

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

1.4. Sample Size Justification

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

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

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

1.5. Randomization and Blinding

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

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

Blinding

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

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

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

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is locked. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1 (date of first dose). If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2.1.1) are the visit windows and the target days for each visit defined in the protocol. A Post-Week 26 window was created to account for subjects who returned at a time that would no longer be considered consistent with a Week 26 measurement.

Table 2.1.1: Visit Windows

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Serum Chemistry and Trough PK	2	Baseline	≤1[b]	1
	3	Week 2	2–25	15
	4	Week 5	26-53	36
	5	Week 10	54-88	71
	6	Week 15	89-123	106
	7	Week 20	124-162	141
	8	Week 26	163- 203	183
	9	Post-Week 26	>203	
All other parameters	2	Baseline	≤1[b]	1
	4	Week 5	2-53	36
	5	Week 10	54-88	71
	6	Week 15	89-123	106
	7	Week 20	124-162	141
	8	Week 26	163-203	183
	9	Post-Week 26	>203	

[a] Relative to the day of the first dose of double-blind study medication.
[b] Up to the first dose of double-blind study medication.

2.2. Pooling Algorithm for Analysis Centers

All centers will be pooled. In other words, center will not be included in any statistical model. If the analyses should involve geographical region, the Regions will be defined by country as follows:

- Europe: UK, Belgium, Sweden, Poland
- North America: Canada, US

2.3. Analysis Sets

2.3.1. All Randomized Analysis Set

The all randomized analysis set is not used in the study.

2.3.2. Efficacy Analysis Sets

- The intent-to-treat (ITT) analysis set will include all subjects who are randomly assigned to a treatment group and have a baseline body weight measurement.
- The modified intent-to-treat (mITT) population includes all ITT subjects who have taken at least one dose of study medication and have at least 1 post-baseline body weight measurement; for subjects randomized to liraglutide, only those who titrate to 3.0 mg will be included in the mITT population.
- The completers' analysis set will consist of all mITT subjects who have completed 26 weeks of treatment (ie, documented in the Treatment Disposition eCRF by the investigators that the subject has completed treatment through the Week 26 visit window).
- The ABPM analysis set will consist of all mITT subjects who have valid baseline and valid post-baseline ABPM readings. If the post-baseline reading was collected after the last dose plus 2 days for liraglutide subjects and 14 days for JNJ64565111 and placebo subjects, the subject will be excluded from the ABPM analysis set.

The primary efficacy analysis, to demonstrate the superiority of JNJ-64565111 compared to placebo on percentage reduction in body weight from baseline to Week 26, as well as all secondary efficacy analyses, will be based on the mITT analysis set.

A secondary analysis of the primary and secondary efficacy endpoints will be based on the ITT population (including data after the on-treatment period). This analysis will include all measurements through the Week 26 visit window. Supportive analyses based on the completers' analysis set will also be performed for the primary endpoint.

2.3.3. Safety Analysis Set

The safety analysis set will include all randomized subjects who have received at least one dose of study drug.

2.3.4. Pharmacokinetics Analysis Set

The PK evaluable (PK) analysis set includes treated subjects (received at least one dose of JNJ-64565111) who have at least one post-baseline PK sample for analysis.

Pharmacokinetics analyses will be performed using the PK analysis set. Analysis will be based on the actual treatment received.

2.3.5. Pharmacodynamics Analysis Set

Pharmacodynamics analyses will use the mITT analysis set. Analysis will be based on the actual treatment received.

2.3.6. Immunogenicity Analysis Set

The immunogenicity evaluable (IE) analysis set includes treated subjects (received at least one dose of JNJ-64565111) who have a sample at baseline and at least 1 post-baseline sample for analysis. Immunogenicity analyses will use this analysis set. Analysis will be based on the actual treatment received.

2.4. Definition of Subgroups

Subgroup analyses may be performed based on the subgroups defined below.

Subgroup	**Definition**
Sex	• female • male
Age	• 18-59 years • 60-70 years
Race	• White • Black or African American • Asian • Other
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino • Unknown • Not reported
Region	• North America • Europe
Baseline BMI	• <40 kg/m^2 • ≥40 kg/m^2
Baseline eGFR	• <90 $mL/min/1.73m^2$ • ≥90 $mL/min/1.73m^2$
Randomization strata	• ABPM sub-study participation: Yes • ABPM sub-study participation: No

For subjects who participate in the ABPM sub-study, the subgroup analysis may be performed based on the history of hypertension (yes/no).

2.5. Study Day and Relative Day

Study Day 1 or Day 1 refers to the day of the first study agent administration on or after the randomization date. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'

2.6. Baseline

Baseline is defined as the last observation prior to the first study agent administration on or after the randomization date.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

A pre-planned interim analysis (IA) will be performed when approximately 90% of subjects have either completed or discontinued prior to 10 weeks of study treatment. This IA will require support from an internal Data Monitoring Committee (DMC) and the analysis will be described in a separate DMC SAP.

The objective of this interim analysis is to identify active treatment groups, if any, associated with safety or tolerability issues and to facilitate planning of the Phase 3 program. There will be no alpha adjustment for unblinded review(s). Additionally, based on ongoing blinded safety reviews by the study team, the study team may ask the DMC to evaluate specific safety data in an unblinded manner.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group, combined JNJ-64565111 treatment group, and overall. In addition, the distribution of subjects by region, country, and site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 4.1.1 presents a list of the demographic variables that will be summarized by treatment group, combined JNJ-64565111 treatment group, and overall for the ITT analysis set, mITT analysis set, safety analysis set, completers' analysis set, and PK analysis set.

Table 4.1.1: Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Waist circumference (cm)	
Pulse rate (bpm)	
Systolic Blood Pressure (mmHg)	
Diastolic Blood Pressure (mmHg)	
Rate pressure product (bpm*mmHg)	
eGFR (mL/min/1.73m^2)	
HbA_{1c}	
FPG (mmol/L)	
Fasting insulin (pmol/L)	
Fasting C-peptide (nmol/L)	
Fasting serum lipids: total cholesterol, triglycerides, high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C)	
IWQOL-Lite physical function domain score	
Beta-hydroxybutyrate (mmol/L)	
Categorical Variables	**Summary Type**
Age (18-30 years, 31-50 years, 51-64 years, and ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Age for analysis (18-59 years and ≥60 years)	
Sex (male, female)	
Race[a] (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, Other)	
Race for analysis (White, Black or African American, Asian, and Other)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported)	
Region (North America, Europe)	
Baseline BMI (<40, ≥40 kg/m2)	
Randomization strata (ABPM sub-study participation: Yes/No)	
Baseline eGFR (<90, ≥90 mL/min/1.73m2)	
Baseline SBP (<140 mmHg, ≥ 140 mmHg)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

4.2. Disposition Information

The number of subjects in the following disposition categories will be summarized by treatment group and overall:

- Subjects randomized;
- Subjects in the ITT analysis set;
- Subjects in the mITT analysis set;
- Subjects in the completers' analysis set;
- Subjects in the mITT analysis set who discontinue from treatment before the Week 26 visit (ie, investigator indicates on the eCRF [treatment disposition page] that the subject discontinued from treatment);
- Subjects in the mITT analysis set who discontinue from study before the Week 26 visit (ie, investigator indicates on the eCRF [trial disposition page] that the subject discontinued from study);

- Subjects in the safety analysis set;
- Reasons for discontinuation of study.

For subjects who discontinue from the study after randomization, the corresponding reasons for (1) discontinuation from the treatment, and (2) discontinuation from the study during the 26-week treatment phase will be summarized.

The distribution of the time to study discontinuation for the 26-week treatment phase will be displayed with Kaplan-Meier curves. Subjects who terminate study participation prematurely at any time will be considered an 'Event' and their date of study discontinuation will be used in the time to event calculation. Subjects who complete the study will be censored on their date of study completion. Descriptive analyses for the time to early discontinuation will be provided.

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent;
- Subjects who terminated study prematurely;
- Subjects who were unblinded during the study period;
- Subjects who were randomized yet did not receive study agent.

4.3. Treatment Compliance

Treatment compliance will be derived based on the information from the study drug administration eCRF page.

Compliance with study medication will be calculated as follows:

- Study agent compliance (%) = 100 x [number of doses taken/total treatment duration in weeks rounded up to nearest integer]
- Open-label Liraglutide compliance (%) = 100 x [number of doses taken/total treatment duration in days].

4.4. Extent of Exposure

Treatment duration will be calculated (in days) based on the dosing schedule as follows:

Study agent: Date of last dose – date of first dose + 8 days

Liraglutide: Date of last dose – date of first dose + 1 day

If the end date of the study medication intake is not known (eg, subject is lost to follow-up), it will be imputed as the earlier of the date of death, disposition date (ie, End of study date, End of Treatment) and 28 days from the date that the last medication kit was dispensed.

Descriptive statistics for treatment duration (N, mean, standard deviation, median, and range) will be presented by treatment group for the safety analysis set. The number and percentage of

subjects who receive study agent will also be summarized by treatment group with the duration in each of the following categories:

- For double-blind treatment phase, <2 weeks, 2 to <6 weeks, 6 to <12 weeks, 12 to <18 weeks, 18 to <24 weeks, and ≥24 weeks

4.5. Protocol Deviations

Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be listed.

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent.

Summaries of concomitant medications will be presented by ATC term and treatment group. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication. In addition, concomitant medications of interest will be presented.

Prior medications will be summarized by treatment group/dose level and ATC term.

5. EFFICACY

The primary analysis of the primary, secondary and exploratory efficacy endpoints of the main study will be based on the mITT analysis set and will include only those post-baseline measurements taken within the 26-week double-blind phase while on treatment. Data collected after the last dose plus 2 days for liraglutide subjects, and after the last dose plus 14 days for JNJ64565111 and placebo subjects will be excluded from the mITT analysis. A secondary analysis of the primary and secondary efficacy endpoints will be based on the ITT analysis set. This analysis will include post-baseline measurements taken within the 26-week double-blind phase regardless of whether on-treatment or off-treatment. Sensitivity analyses for the primary efficacy endpoint using the completers' analysis set will also be performed.

Regardless of the actual treatments the subjects received, efficacy data will be analyzed according to the initial randomization assignment for the treatment (26-week) phase.

5.1. Analysis Specifications

5.1.1. Level of Significance

Unless otherwise specified, all statistical tests will be interpreted at a 2-sided significance level of 5% and all confidence intervals at a 2-sided confidence level of 95%.

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

5.1.2. Data Handling Rules

Unlike other assessments which are scheduled to be collected once at each visit, three consecutive readings of the SBP, DBP and pulse rate will be measured (at intervals of at least 1 minute apart) and recorded. The average of the multiple measurements will be computed at each visit for all subjects and this averaged value will be used in all the analyses and summaries of blood pressure and pulse rate.

Ambulatory Blood Pressure Monitoring (ABPM) Sub-study

The 24-hour ABPM sub-study will be performed in a subset of approximately 120 subjects at selected sites. The ABPM blood pressure and pulse rate readings will be collected over a 24-hour period at each of these 2 time points: 1 or 2 days prior to the Day1/Randomization visit and 1 or 2 days prior to the Week 26/ EOT.

The ABPM devices are calibrated to record the blood pressure (SBP and DBP) and pulse rate measurements every 20 minutes during daytime hours and every 30 minutes during nighttime hours. These blood pressure measurements will be used to determine:

- mean 24-hour SBP, mean daytime SBP, mean nighttime SBP
- mean 24-hour DBP, mean daytime DBP, mean nighttime DBP
- mean 24-hour pulse rate, mean daytime pulse rate, mean nighttime pulse rate
- mean 24-hour rate pressure product, mean daytime rate pressure product, mean nighttime rate pressure product

To derive the above means, the following steps will be taken:

- Hourly means will be averaged to derive the 24-hour means
- Hourly means that account for data collected from 8:00 am to 10:59 pm will be averaged to derive daytime mean
- Hourly means that account for data collected from 11:00 pm to 7:59 am will be averaged to derive the nighttime mean.

The 24-hour ABPM recording will be considered 'valid' if two rules are met:

1. There are at least 42 valid scheduled readings within the 22 hours of recording time.

2. There are no more than 2 consecutive hours of missing data (readings) within the 22 hours of recording time.

Only valid readings will be included in the ABPM analysis. Subjects without valid reading post-baseline will be excluded from the analysis.

Details regarding the handling of missing and partial dates, the derivation of PRO measures will be contained in the data presentation specifications (DPS).

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint will be the percentage change in body weight from baseline to Week 26.

5.2.2. Estimand

Population: non-diabetic, obese subjects in the mITT analysis set who are ≥18 and ≤70 years of age and have a BMI ≥35 to ≤50 kg/m^2

Variable: percentage change in body weight from baseline to Week 26

Population-level summary: mean percentage change in body weight from baseline to Week 26

5.2.3. Analysis Methods

Primary Analysis

The primary analysis of the primary endpoint will be based on the mITT population and will use a mixed model for repeated measures (MMRM). The analysis will use the observed data through Week 26 while on treatment and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the fixed, continuous, covariates of baseline body weight and baseline-by-visit interaction. Data collected after the last dose plus 14 days for 5111/placebo subjects (2 days for liraglutide subjects) will be excluded from the mITT analysis.

An unstructured covariance will be used to model the within-patient errors. The treatment comparisons will be made between each of the JNJ-64565111 treatment groups and placebo at Week 26.

Secondary Analysis

A secondary analysis of the primary endpoint will be based on the ITT population using all observed data (on or off-treatment) and will employ pattern mixture models using multiple imputation methods. Responses for subjects who discontinued from the study earlier than

Week 26 will be imputed based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. The imputation will be done within groups defined by randomized treatment. A MMRM analysis will be used with fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the fixed, continuous, covariates of baseline body weight and baseline-by-visit interaction. The treatment comparisons between each of the JNJ-64565111 treatment groups and placebo will be made at Week 26. Copy control imputation may be used as an alternative to a retrieved dropout approach.

Supportive Analyses

Sensitivity analyses for the primary efficacy endpoint will be performed based on the completers' analysis set using the same mixed model for repeated measures as in the primary analysis.

The primary analysis will also be repeated with the addition of strata (ABPM substudy participation) as a fixed effect to determine if there is a difference in the point estimates after adjustment for strata in the model.

Subgroup Analyses

Additional analyses of the primary efficacy endpoint in the mITT analysis set will be performed to assess consistency of treatment effect on percent weight loss for the subgroups defined in Section 2.4 (if there are at least 100 subjects in the subgroup). The interaction of treatment with each of the subgroups will be analyzed based on the MMRM model for the primary efficacy analysis with the addition of the subgroup and the appropriate corresponding interaction terms. If an interaction is observed (2-sided significance level of 0.10), then further evaluations will be performed to assess and explain the nature of the interaction [quantitative or qualitative interaction]. The percent change from baseline and the 95% CI for differences between each dose of JNJ-64565111 and liraglutide compared to placebo will be presented for the subgroups.

Exploratory Analyses

Additional analysis using an MCP-Mod (Multiple Comparison Procedure – Modelling) approach will be performed to explore the dose response relationship.

The exploratory analysis of the assessments between the JNJ-64565111 treatment groups and liraglutide on the percentage change in body weight at Week 26 will also be performed. The same analysis models used for the comparisons with placebo on the primary efficacy endpoint will be used for these assessments. For subjects on liraglutide, the observed data through Week 26 while on treatment will be used. Nominal p-values will be provided.

5.3. Major Secondary Endpoints

5.3.1. Definition

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

5.3.2. Analysis Methods

Primary Analysis

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

The categorical secondary efficacy endpoint (i.e., proportion of subjects with ≥5% weight loss, proportion of subjects with ≥10% weight loss at Week 26) will be analyzed using the mITT analysis set such that only subjects with observed Week 26 on-treatment weight measurements are eligible to be considered responders (either ≥5% weight loss or ≥10% weight loss) and subjects without Week 26 on-treatment weight measurements will be considered non-responders. A logistic regression model will include the fixed, categorical effect of treatment and the continuous covariate of baseline weight. The odds ratio and associated adjusted p-value for the treatment comparison between each of the JNJ-64565111 treatment groups versus placebo at Week 26 based on this model will be provided.

Secondary Analysis

A secondary analysis of the secondary endpoints will be based on the ITT population using all observed data (on or off-treatment) and will employ pattern mixture models using multiple imputation methods based on information from retrieved dropouts as described above. For the categorical endpoints, response status will be determined from the imputed continuous response based on subjects who discontinued treatment prematurely but subsequently provided off-treatment measurements. Copy control imputation may be used as an alternative to a retrieved dropout approach.

Exploratory Analyses

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

5.4. Exploratory Efficacy Variable(s)

5.4.1. Definition

Exploratory Endpoints

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

- the change from baseline in fasting C-peptide
- the changes from baseline in HOMA-B and HOMA-IR
- the change from baseline in SBP
- the change from baseline in DBP
- the change from baseline in pulse rate
- the change from baseline in pulse-pressure product
- in a subset of subjects participating in the 24-hour ABPM assessment, the changes from baseline in 24-hour SBP, DBP, pulse rate and pulse-pressure product
- the change from baseline in scores on the IWQOL-Lite,[2,3] single item Ease of Weight Management, and PAM
- the change from baseline in scores on the ERCQ and the PROMIS physical function short form 8b (PROMIS SF 8b). (Note: the Patient Global Impression Status [PGIS] and Patient Global Impression of Change [PGIC] will be used to calculate responder definitions for these new instruments only and are not exploratory objectives).

5.4.2. Analysis Methods

The continuous exploratory efficacy endpoints (Change from baseline in BMI, waist circumference, total cholesterol, LDL-C, HDL-C, triglycerides, FPG, fasting insulin, C-peptide, SBP, DBP, pulse rate, pulse rate product) will be analyzed using a MMRM model similar to that used to analyze the primary efficacy endpoint. An ANCOVA model will be used for endpoints with only one planned post-baseline timepoint.

Shift tables will be used to summarize obesity class (Class I = 30 kg/m^2 – 34.9 kg/m^2; Class II = 35 kg/m^2 – 39.9 kg/m^2; Class III = ≥ 40 kg/m^2) at baseline vs. end of treatment. Descriptive statistics (N, mean, standard deviation, median, and range) for the actual values and the changes from baseline will be presented by treatment group and visit for all exploratory endpoints including ‘mean 24-hour SBP’, ‘mean 24-hour DBP’, ‘mean daytime SBP’, ‘mean daytime DBP’, ‘mean nighttime SBP’, and the ‘mean nighttime DBP ’, ‘mean 24-hour pulse rate’, ‘mean daytime pulse rate’, ‘mean nighttime pulse rate’, ‘and mean 24-hour RPP. RPP is defined as the product of heart rate and systolic blood pressure. Changes from baseline for each endpoint at the last on-treatment measurement will be analyzed using an ANCOVA model in the mITT analysis set. The analysis will be based on observed data and will include the fixed, categorical effects of treatment as well as the fixed, continuous covariate of baseline value. The treatment comparisons for the JNJ-64565111 versus placebo will be made at the last on-treatment measurement.

For ABPM sub-study participants, baseline body weight, percentage change and absolute change from baseline in body weight will be summarized by treatment and visit.

A MMRM model similar to that used to analyze the primary efficacy endpoint will be used to analyze the exploratory PRO endpoints for endpoints with more than one planned post-baseline timepoint.

The other PRO assessments will be described in a separate SAP for PROs.

6. SAFETY

All safety analyses and summaries will be based on the safety analysis set (Section 2.3.3). Safety data will be analyzed according to the predominant treatment received, in the event that a subject received a treatment other than that to which they were randomly assigned to receive. The predominant treatment is defined as the treatment to which the subject was exposed for the greatest duration during the core treatment phase.

The evaluation of safety will be based on the incidence of AEs and changes in clinical laboratory test results and vital sign results (blood pressure, pulse rate). There will be no imputation of missing values for clinical laboratory test results and vital sign measurements in the safety analyses and there will be no hypothesis testing for results from safety analyses. Summaries of AEs, clinical laboratory test results, and vital sign results will be provided by treatment group and for the combined JNJ-64565111 treatment group.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent AE (TEAE) is defined as an adverse event with an onset after the initiation study medication and before the last study medication date of the double-blind (26-week) treatment phase for plus 28 days for liraglutide subjects, and plus 35 days for JNJ64565111 and placebo subjects. AEs with a start date prior to initiation of double-blind study medication which are subsequently reported to have either an increase in intensity or change in attribution in relationship to study medication (ie, no attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs.

If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be provided by preferred term, grouped by system organ class (SOC), and presented by treatment group. In addition, comparisons between treatment groups may be provided as needed.

Summary tables will be provided for:

- AEs
- AEs leading to discontinuation
- Drug-related AEs
- Drug-related AEs leading to discontinuation

- Serious AEs (SAEs)
- Serious AEs leading to discontinuation
- Serious drug-related AEs leading to discontinuation and deaths
- AEs by system organ class
- AEs by severity
- AEs by relationship to study agent: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator)
- AEs by the action taken regarding the study medication
- AEs by the outcome

In addition to the summary tables, listings will be provided for subjects who had:

- SAEs
- AEs leading to discontinuation

Incidence of other treatment-emergent adverse events of special interest will be summarized.

Deaths will be displayed by actual treatment received. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent (yes/no)

A listing of subjects who died will be provided.

As a screening tool, the 95% CIs for percentage difference between JNJ-64565111 and placebo will be provided for the AEs which are reported in at least four or more subjects in any treatment group during the treatment phase. Four (rule-of-4) is chosen based on the recommendation from the Safety, Planning, Evaluation, and Report (SPERT).[1] No multiplicity adjustment will be applied. The exclusion of "0" in the 95% CI around the difference in incidence (JNJ-64565111 compared to placebo) for a particular AE does not necessarily imply that the higher incidence is related to drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment.

Adverse events that are identified by the above screening procedure will be subject to further evaluation. The additional assessment may include some or all of the following, comparing JNJ-64565111 and placebo

1. Investigator assessed relationship of AE to study drug, investigator assessed intensity of AE
2. Time to AE relative to start of double-blind study medication, duration of AE, action taken on study drug/occurrence of AEs leading to discontinuation

3. Other relevant safety information such as observations in other trials

Adverse Events of Interest

Protocol prespecified AEs of interest included MACE, hypotension-related AEs, pancreatic events, calcitonin elevation, and thyroid neoplasm. Prior to study unblinding, additional AEs of interest were identified including nausea, vomiting, diarrhea, and AEs of injection site reaction. Since investigators may have reported the same clinical condition using different AE terms, prior to study unblinding a list of reported terms that are suggestive of the AEs of nausea, vomiting, diarrhea, injection site reactions, and pancreatic-related AEs was generated. These preferred terms were used to generate combined analyses for each of these specific AEs of interest.

6.2. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set. Laboratory data will be summarized for each type of laboratory test listed in Attachment 1. Normal reference ranges for each test will also be provided.

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points. Descriptive statistics will be presented based on measurements on study medication, including up to a maximum of 2 days after the last dose of study medication for liraglutide subjects and 14 days for JNJ64565111 and placebo subjects, as well as all measurements regardless of the time of the last dose of double-blind study drug for subjects who discontinue from treatment before Week 26. Summaries based on both standard units (SI) and conventional units will be provided.

Change from baseline to scheduled time point as well as the 95% CI will be summarized for chemistry, hematology, and urinalysis (pH, and specific gravity) tests and displayed by visit and treatment group.

Number and percentage of subjects with post-baseline clinically important laboratory values will be presented by treatment group.

The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria will be summarized for these laboratory analytes. The 95% CI for the percentage difference between the treatment groups will be provided for each treatment and combined JNJ64565111 treatment group for the PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided. The criteria for PDLC values are listed in Attachment 2.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including pulse, blood pressure (systolic and diastolic) will be summarized at each assessment time point. Changes from Baseline will be summarized for the 26-week treatment phase. Descriptive statistics (mean, standard deviation, median, interquartile range [IQR], minimum and maximum) will be presented at each scheduled time point, including the 95% CI for the change from baseline for the 26-week core treatment phase. The descriptive

statistics will be presented based on measurements on study medication, including up to a maximum of 2 days after the last dose of study medication for liraglutide subjects and 14 days for JNJ64565111 and placebo subjects, as well as all measurements regardless of the time of the last dose for subjects who discontinue from treatment before Week 26. The pulse and blood pressure measurements will be based on the average of the consecutive sitting pulse and blood pressure readings that were to be collected at each visit.

The percentage of subjects with specific treatment-emergent vital sign values meeting PDLC criteria (Attachment 2) will be summarized for these vital sign parameters. The 95% CI for the percentage difference between the treatment groups will be provided for each treatment and combined JNJ64565111 treatment group for the PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided.

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

6.4. Electrocardiogram

A 12-lead ECG will be performed during screening. No summary is planned.

7. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMICS

7.1. Pharmacokinetics

Pharmacokinetics (PK) samples for measuring serum JNJ-64565111 concentrations will be collected from all subjects at the specified visits as shown in the schedule of events of the protocol. In all subjects randomly assigned to JNJ-64565111 or matching placebo (but not in subjects randomly assigned to open-label liraglutide), venous blood samples will be collected according to the Time and Events Schedule for determination of serum trough concentrations of JNJ-64565111 to assess attainment of steady state concentrations. In addition, a sample at the 4-week safety follow-up visit will also be collected in all subjects. On the days of the trough clinic visits at which PK samples are to be obtained, subjects are not to inject the study drug before arriving at the clinic. In addition to the trough samples and a post-treatment sample in all subjects, a subset of subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample. The non-trough PK visit will occur at selected sites and will involve approximately 180 subjects (approximately 45 subjects each in the placebo, JNJ-64565111 5 mg, JNJ-64565111 7.4 mg, JNJ-64565111 10 mg groups). All PK evaluations will be based on the PK analysis set. No imputation for missing concentration data will be performed.

The data analysis of trough and non-trough serum JNJ-64565111 concentrations includes the following:

- Tabular summary of serum JNJ-64565111 concentrations at each PK visit by treatment group.
- Tabular summary of serum JNJ-64565111 concentrations at each visit by treatment group and body weight tertiles at baseline.

- Proportion of subjects without detectable serum JNJ-64565111 concentration at each visit by treatment group.
- Median trough, non-trough, and week 30 temporal serum JNJ-64565111 concentrations plotted over time by treatment group.
- Median trough serum JNJ-64565111 concentrations plotted over time by treatment group to assess attainment of steady-state.

In addition, the relationship between serum JNJ-64565111 concentrations, and antibody to JNJ-64565111 status, safety and efficacy may be explored using graphical displays. The proportion of ≥5% and ≥10% weight loss response rates and % weight loss at Week 26 will be presented in a bar graph by the corresponding serum JNJ-64565111 concentration quartiles at Week 26 for subjects treated with JNJ-64565111.

For summary statistics of serum JNJ-64565111 concentrations, concentration values below the lower limit of quantification will be treated as zero. Once a subject meets one of the following dosing deviation criteria, the subject's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

- Discontinue SC study agent administrations.
- Skipped an SC administration.
- Received an incomplete/ incorrect SC dose.
- Received an incorrect SC study agent.
- Received an additional SC dose.

In addition, if a subject has an administration more than 4 days earlier or later than the scheduled dosing date, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For the Week 26 visit, if the PK sampling time deviates more than 4 days earlier or later than the scheduled date, the PK concentration at this visit will be excluded from the by-visit data analyses.

The conditions under which to exclude measurements from PK analysis:

- If date/time of Baseline sample is after date/time of first dose, then exclude the Baseline sample
- If Day 4 sample is >8 days after 1st dose, then exclude the Day 4 sample
- If date of Week 2 sample – date of previous dose **before date** of Week 2 sample is < 3 days or > 11 days, then exclude Week 2 sample
- If date of Week 5 sample – date of previous dose **before date** of Week 5 sample is < 3 days or > 11 days, then exclude Week 5 sample
- If date of Week 10 sample – date of last dose **before date** of Week 10 sample is < 3 days or > 11 days, then exclude Week 10 sample

- If date of Week 15 sample – date of last dose **before date** of Week 15 sample is < 3 days or > 11 days, then exclude Week 15 sample
- If date of Week 20 sample – date of last dose **before date** of Week 20 sample is < 3 days or > 11 days, then exclude Week 20 sample
- If relative Study Day of Week 26 sample is < Day 178 or >Day 186 then exclude Week 26 sample
- If relative Study Day of Week 30 sample is < Day 206 or >Day 214 then exclude Week 30 sample
- If subject discontinues treatment early, then exclude the "Week 30" or "4 Week Follow-up" PK sample.

Population PK analyses will be performed to characterize the population PK parameters based on the available JNJ-64565111 concentration data obtained through the Week 30 visit. Sparse PK data from the current study may be pooled with previous Phase 1 data with rich PK profiles to allow estimation of structural PK parameters. The population pharmacokinetic approach will also be used to identify and quantify any significant covariates such as demographic characteristics (including but not limited to body weight, ethnic origin, sex, and age) and concomitant medications that have substantial impact on the population pharmacokinetics of JNJ-64565111 in subjects with severe obesity. A detailed analysis plan for population PK analysis will be developed separately, and a stand-alone technical report will be written to summarize the results of the population PK analysis.

7.2. Immunogenicity

Blood samples will be collected to examine the formation of antibodies to JNJ-64565111 at the specified visits (Day 1, Weeks 5, 10, 15, 26, and 30) as shown in the schedule of events of the protocol. For subjects who discontinue SC study agent administrations, samples will be collected at their 4-week safety follow-up visit.

The data analysis of antibodies to JNJ-64565111 will be summarized if sufficient numbers of subjects are positive for antibodies and will include the following:

- The antibody status (positive, negative) of subjects will be summarized by JNJ-64565111 treatment groups. For subjects who discontinue SC study agent administrations and complete 4-week safety follow-up, a listing of their antibody status will be presented.
- The relationship between antibody to JNJ-64565111 status and efficacy and safety may be assessed at Week 26.
- ≥5% and ≥10% weight loss response rates and % weight loss at Week 26 by antibody to JNJ-64565111 status and treatment group
- Injection site reaction by antibody to JNJ-64565111 status and treatment group.
- The relationship between antibody to JNJ-64565111 status at Week 10 and antibody to JNJ-64565111 status at Week 26 will be explored.
- The onset and duration of antibody to JNJ-64565111

- Figure of median serum JNJ-64565111 concentrations by antibody to JNJ-64565111 status.

Other analyses may be performed to verify the stability of antibodies to JNJ-64565111 and/or further characterize the immunogenicity of JNJ-64565111.

7.3. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between serum JNJ-64565111 concentrations and % weight loss may be explored and results will be reported in an independent technical report.

REFERENCES

1. Crowe, B.J. et al., 2009, Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clin Trials 6, 430-40.
2. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity Obes Res 2001; 9(2):102-111.
3. Kolotkin RL, Crosby RD. Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-Lite) in a community sample. Quality of Life Research 2002; 11: 157-171.

ATTACHMENTS

ATTACHMENT 1 CLINICAL LABORATORY TESTS

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

- Hematology Panel

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

- Serum Chemistry Panel

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

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

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

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

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

Estimated Glomerular Filtration Rate (eGFR)

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

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

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

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

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

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

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

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

ATTACHMENT 2 PRE-DEFINED LIMIT OF CHANGE (PDLC) CRITERIA FOR LABORATORY TESTS

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
Albumin	Composite: <LLN and >25% decrease from BL
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Amylase	Absolute Value: >2X ULN
	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
Beta-Hydroxybutyrate	Absolute value> 20.822 mg/dL (>2.0 mmol/L)
Bilirubin	Composite: >ULN and > 25% increase from BL
	Absolute Value: >2XULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcitonin	Absolute Value: >20 ng/L (>5.85 pmol/L)
	Absolute Value: >50 ng/L (>14.63 pmol/L)
	Absolute Value: >100 ng/L (>29.26 pmol/L)
Calcium	Composite: >ULN and >10 % increase from BL
Creatinine Kinase	Absolute Value: >1000 U/L
eGFR	Composite: < 80 and decrease>30% from BL
	Change: decrease>50% from BL
Lipase	Absolute Value: >2X ULN
	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
Magnesium	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Phosphorus	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase >5 mEq/L or more from BL
	Absolute Value: <125 mEq/L
Uric Acid	Composite: <LLN and >25% decrease from BL
HEMATOLOGY	
Hemoglobin	Change: ≥2 g/dl decrease from BL
	Change: ≥2 g/dL increase from BL
Platelets	Composite: >ULN and increase >25% from BL
White Blood Count	Composite: < LLN and >25% decrease from BL
	Composite: > ULN and >50 % increase from BL
VITAL SIGNS	
Pulse Rate	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥90, ≥100 beats per minute
	Changes from baseline >30 bpm, >50 bpm
	Absolute value ≥120 bpm and >30 bpm increase from baseline
	Absolute value ≤50 bpm and >20 bpm decrease from baseline
	Decreases from baseline >5, >10, >15, >20 bpm at consecutive visits
	Increases from baseline >5, >10, >15, >20 bpm at consecutive visits

Laboratory Test	Parameter for ANY value and LAST value
Systolic Blood Pressure	Composite: ≥20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥20 mm Hg increase from BL and ≥160 mm Hg
	Composite: ≥30 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥30 mm Hg increase from BL and ≥160 mm Hg
	Decreases from baseline >5, >10, >15, >20, >25, >30 mmHg at consecutive visits
	Increases from baseline >5, >10, >15, >20, >25, >30 mmHg at consecutive visits
Diastolic Blood Pressure	Composite: ≥15 mm Hg decrease from BL and ≤50 mm HG
	Composite: ≥15 mm Hg increase from BL and ≥100 mm Hg
	Composite: ≥20 mm Hg decrease from BL and ≤50 mm HG
	Composite: ≥20 mm Hg increase from BL and ≥100 mm Hg
	Decreases from baseline >5, >10, >15, >20, >25, >30 mmHg at consecutive visits
	Increases from baseline >5, >10, >15, >20, >25, >30 mmHg at consecutive visits

ATTACHMENT 3 ADVERSE EVENTS OF INTEREST

In order to support the additional assessment of particular categories of adverse events of interest, a list of selected preferred or high level terms have been created. A blinded review prior to database lock was to be performed to assure that no reported term suggestive of the AE of interest was omitted. AEs of interest include:

- Vomiting
- Diarrhea
- Nausea
- Pancreatic events
- Injection site reactions

The list of preferred and high-level terms for the pre-specified adverse events is provided in EDMS-ERI-181673715.