Janssen Research & Development

Statistical Analysis Plan

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

Protocol 64565111OBE2002; Phase 2b
AMENDMENT 1

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

Status: Approved
Date: 19 April 2019
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-ERI-166155513, 2.0

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.
Abbreviations	Added abbreviation of ANCOVA, AHA and ATC. Remove abbreviations that are not in the body of the text. Minor corrections were made for AE(s), PRO, and PROMIS SF 10a.
1	Change the Clinical Protocol JNJ-64565111OBE2002 date to 5 April 2018.
2.1	Visit windows now include post-Week 12 to account for subjects brought back for visits to reduce Lost To Follow Ups.
2.2	Remove Section 2.2 Pooling Algorithm for Analysis Centers
2.2.2	Refined mITT Analysis Set definition to include subjects taking at least one dose of study medication.
2.2.2	Clarify that the Completers' Analysis Set is defined by the Treatment Disposition eCRF status.
2.3	Remove Region because this study is conducted in the US only. Remove Ethnicity, Baseline fasting HOMA-B, and Baseline eGFR to reduce the number of subgroup analyses. A minor correction for the baseline HbA_{1c} categories was made.
2.3, 4.1	Correct variable name for HOMA-B and HOMA-IR.
4.1	Demographics tables will be generated for 5 analysis sets: ITT, mITT, Safety, PK, and Completers. Added variables rate pressure product (bpm*mmHg), Beta-hydroxybutyrate (mmol/L). Removed ratios of LDL-C/LDL-C. Added unit (%) for HbA_{1c}. A minor correction for baseline HbA_{1c} categories was made.
4.2	Screen failures will not be summarized. Protocol deviations will be listed that may include deviations related to medication dispensed. Removed the bullet of "reasons for discontinuation from study" as it is redundant with the paragraph below.
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.
4.2, 4.3	Changed "study agent" to "treatment" to keep the consistency through the SAP.
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. Removed "study agent" from the second paragraph of the section. Replaced "treatment duration prior to rescue medication" and "treatment duration" for "treatment duration" and "overall duration", respectively.
4.5	Protocol deviations, as identified by the Study Team, will be listed but not summarized.
5.0, 5.2.3, 5.4.2	"Data collected after the last dose plus 7 days" changed to "Data collected after the last dose plus 14 days will be excluded from the mITT analysis." This change is based on what is known about PK.
5.1.1	Clarify adjusted p-values will be presented comparing each JNJ-64565111 dose to placebo in the summary tables.
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	Change the minimum number of subjects from 80 to 40 as the threshold to perform subgroup analyses. Clarified 2- and 3-way interaction terms with treatment will be included in the model.
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.
1.3, 5.3.1, 5.4.1	Reworded the efficacy endpoints to reduced awkwardness of phrasing (e.g., "absolute change from baseline in body weight" from "absolute change in body weight from baseline").
5.3.2, 5.4.2	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	Added lists of endpoints for MMRM and ANCOVA analyses. Added shift table for obesity class.
5	All efficacy analyses for non-glycemic endpoints will be performed regardless of rescue medication. Analyses of glycemic endpoints (i.e., HbA_{1c}, FPG, fasting insulin, HOMA-B, HOMA-IR) will accordingly be based on a prior to rescue medication analysis.

SECTION(S)	CHANGE and RATIONALE
6	Reference to Section 2.3.4 should be 2.2.3.
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 should be 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.
7.1	The details under which measurements should be excluded from the PK analysis are provided.
References	Added references 4 and 5 for IWQOL-Lite.
ATCH 2	Added PDLCs for calcitonin, amylase and lipase.
ATCH 2	Beta-Hydroxybutyrate above 20.822 mg/dL will be flagged as PDLC.
ATCH 3	Refer to Excel files; reference in ERIS.

ABBREVIATIONS

β-hCG	Serum β-human chorionic gonadotropin
ADA	anti-drug antibody
AE(s)	Adverse event(s)
AHA	Antihyperglycemic agent
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
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
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
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
PK	Pharmacokinetics
PRO	Patient-reported outcome (paper or electronic as appropriate for this study)
PROMIS SF 10a	PROMIS physical function Short Form 10a
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
T2DM	Type 2 diabetes mellitus
TEAE(s)	Treatment-emergent adverse event(s)
ULN	Upper limit of normal
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-64565111OBE2002. This SAP is based on the Clinical Protocol JNJ-64565111OBE2002 dated 5 April 2018. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures and listings) will be provided in a separate document entitled Data Presentation Specifications (DPS). A separate Data Monitoring Committee (DMC) SAP will describe the data analysis for DMC reviews.

1.1. Trial Objectives

Primary Objectives

The primary objectives are to assess the effects of JNJ-64565111 compared with placebo in severely obese subjects with Type 2 Diabetes Mellitus (T2DM) after 12 weeks of treatment on:

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

1.2. Trial 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 antihyperglycemic agent (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 (date of first dose), 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).

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

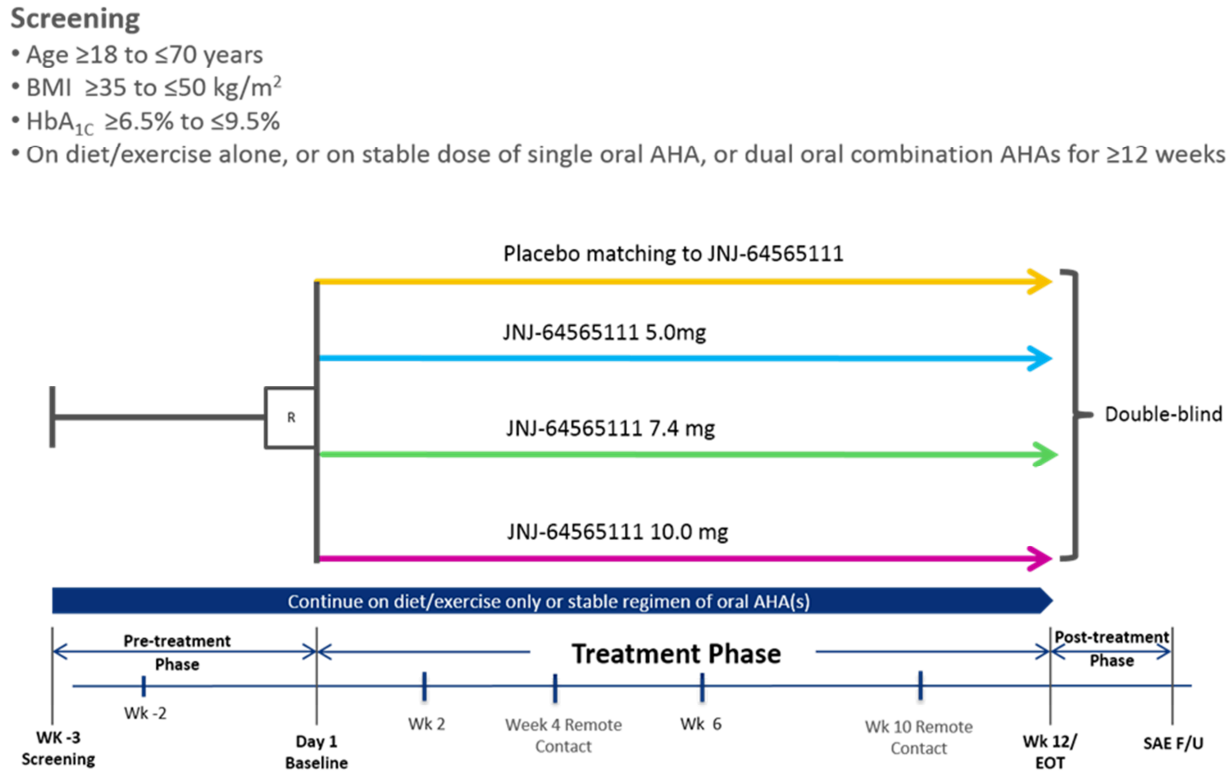
only) are allowed as rescue medication; GLP-1 agonists and short-acting or intermediate insulins are not allowed as rescue medication.

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

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 severely obese T2DM subjects, at least one dose JNJ-64565111 compared with placebo at 12 weeks leads to a greater:

Primary:

- percentage reduction from baseline in body weight

Secondary:

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

1.4. Sample Size Justification

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 at least one dose of JNJ-64565111 leads to greater percentage reduction in body weight at 12 weeks 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 family-wise 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%.

1.5. Randomization and Blinding

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, HbA_{1c}, 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 locked. 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.

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 12 window was created to account for subjects who returned at a timepoint after the Week 12 visit window.

Table 2.1.1: Visit Windows

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
All	2	Baseline	≤1[b]	1
	3	Week 2	1[c]–28	15
	4	Week 6	29-64	43
	5	Week 12	65-105	85
	6	Post-Week 12	≥106	

[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. Analysis Sets

2.2.1. All Randomized Analysis Set

The all randomized analysis set will include all subjects who are randomly assigned to a treatment group.

2.2.2. 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) analysis set includes all ITT subjects who have taken at least one dose of study medication and have at least 1 post-baseline body weight measurement.
- The completers' analysis set will consist of all mITT subjects who have completed 12 weeks of treatment (i.e., documented in the Treatment Disposition eCRF by the investigators that the subject has completed treatment through the Week 12 visit window).

The primary efficacy analysis, to demonstrate the superiority of JNJ-64565111 compared to placebo on percentage reduction in body weight from baseline to Week 12, 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 initiation of rescue medication and data after the on-treatment period). This analysis will include all measurements through the Week 12 visit window. Supportive analyses based on the completers' analysis set will also be performed for the primary endpoint.

2.2.3. Safety Analysis Set

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

2.2.4. Pharmacokinetics Analysis Set

The 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 actual treatment received.

2.2.5. 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.

2.3. Definition of Subgroups

Subgroup analyses may be performed as defined below when there are at least 40 subjects within each subgroup category.

Subgroup	Definition
Sex	• female • male
Age	• 18-59 years • 60-70 years
Race	• White • Black or African American • Asian • Other
Baseline BMI	• <40 kg/m2 • ≥40 kg/m2
Baseline HbA_{1c}	• <8% • 8% to <9% • 9% to <10% • ≥10%
Baseline fasting HOMA-IR	• ≤ the median • > the median

2.4. 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'.

2.5. Baseline

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

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

A pre-planned interim analysis was performed in Study 64565111OBE2001; at the time of the interim analysis, available unblinded safety data from this study (64565111OBE2002) was reviewed by the DMC. These analyses were described in a separate DMC SAP.

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, a frequency table of the number of subjects by site will be presented.

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)	
Duration of diabetes (years)	
Duration of oral antidiabetic treatment prior to study entry (years)	
HOMA-B	
HOMA-IR	
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)	
Baseline BMI (<40, ≥40 kg/m^2)	
Baseline HbA_{1c} (<8%, 8% to <9%, 9% to <10%, ≥10%)	
Baseline fasting HOMA-B (≤ the median, > the median)	
Baseline fasting HOMA-IR (≤ the median, > the median)	
Baseline eGFR (<90, ≥90 mL/min/1.73m^2)	
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 12 visit (i.e. investigator indicates on the eCRF [treatment disposition page] that the subject discontinued from the treatment);
- Subjects in the mITT analysis set who discontinue from study before the Week 12 visit (i.e., investigator indicates on the eCRF [trial disposition page] that the subject discontinued from study);
- Subjects in the mITT analysis set who receive glycemic rescue therapy (documented in the eCRF by investigator) before the Week 12 visit;
- Subjects in the safety analysis set

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 12-week treatment phase will be summarized.

The distribution of the time to study discontinuation for the 12-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 from treatment
- Subjects who discontinued from the study prematurely
- Subjects who were unblinded during the study period
- Subjects who were randomized but did not receive treatment.

4.3. Treatment Compliance

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

Treatment compliance will be calculated as follows:

> Treatment compliance (%) = 100 x [number of doses taken/total treatment duration in weeks rounded up to nearest integer]

4.4. Extent of Exposure

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

> Date of last dose – date of first dose + 8 days

If the end date of the study medication intake is not known (e.g., subject is lost to follow-up), it will be imputed as the earlier of: (1) the date of death, (2) the disposition date (i.e., end of study date, end of treatment date), or (3) 28 days from the date that the last medication kit was dispensed.

Descriptive statistics (N, mean, standard deviation, median, and range) will be presented by treatment group for treatment duration prior to rescue medication (excluding the duration after initiation of rescue medications), and the overall treatment duration (including after initiation of rescue medication) for the safety analysis set.

The number and percentage of subjects who receive treatment will also be summarized by treatment group with the duration in each of the following categories:

- For the entire double-blind treatment phase, <2 weeks, 2 to <6 weeks, 6 to <10 weeks, and ≥10 weeks

4.5. Protocol Deviations

Subjects with major protocol deviations will be identified prior to database lock and provided in a listing.

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 Anatomical Therapeutic Chemical (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 will be based on the modified intent-to-treat (mITT) analysis set. Only those measurements taken up to the last dose of study drug plus 14 days will be included in the analysis. 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 post-baseline measurements taken within the 12-week double-blind phase regardless of rescue medication initiation, and regardless of whether on or off-treatment. 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.

5.1. Analysis Specifications

5.1.1. Level of Significance

The type I error rate will be strongly controlled at α=5% for each of the primary endpoint and secondary endpoints. The Hochberg approach will be used to adjust for the multiplicity of the comparisons of each of the JNJ-64565111 doses versus placebo for each of the primary and major secondary efficacy endpoints. Adjusted p-values will be provided.

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%. Nominal p-values will be presented for endpoints other than those described above.

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. Details regarding the handling of missing and partial dates, the derivation of Patient-Reported Outcomes (PRO) measures are described 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 12.

5.2.2. Estimand

Population: diabetic, obese subjects in the mITT analysis set who are ≥18 and ≤70 years of age, have a BMI ≥35 to ≤50 kg/m^2, and have a HbA_{1c} ≥6.5% to ≤9.5%.

Variable: percentage change in body weight from baseline to Week 12

Population-level summary: mean percentage change in body weight from baseline to Week 12.

5.2.3. Analysis Methods

Primary Analysis

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 14 days). 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.

Secondary Analysis

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 and adjusted p-values will be provided. 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.

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 2.3 (if there are at least 40 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 2- and 3-way interaction terms with treatment. If an interaction is observed (2-sided p-value <0.10), then

further evaluations will be performed to assess and explain the nature of the interaction [quantitative or qualitative interaction]. The percentage change from baseline and the 95% CI for differences between each dose of JNJ-64565111 compared to placebo will be presented for the subgroups.

Exploratory Analyses

Additional analysis using a MCP-Mod (Multiple Comparison Procedure – Modelling) approach[1,2] will be performed to explore the dose response relationship.

5.3. Major Secondary Endpoints

5.3.1. Definition

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

5.3.2. Analysis Methods

Primary Analysis

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 at Week 12 will be analyzed using the mITT analysis set. Only subjects with observed data at Week 12 while on treatment (up to the last dose of study drug plus 14 days) are eligible to be considered responders (≥5% weight loss). Subjects without an on treatment weight measurement at Week 12 will be considered non-responders. A logistic regression model including treatment as a fixed effect, and baseline weight as a covariate will be used for the analysis. The odds ratio and adjusted 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.

Secondary Analysis

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. Copy control imputation may be used as an alternative to a retrieved dropout approach.

5.4. Exploratory Efficacy Variable(s)

5.4.1. Definition

The following exploratory efficacy endpoints at Week 12 will also be analyzed:

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

- the change from baseline in BMI
- the change from baseline in waist circumference
- the change from baseline in glycated hemoglobin (HbA_{1c})
- the change from baseline in fasting plasma glucose (FPG)
- the change from baseline in fasting insulin
- the change from baseline in fasting C-peptide
- the changes from baseline in Homeostasis Model Assessment for B cell function (HOMA-B) and HOMA-insulin resistance (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 rate pressure product
- the change from baseline in fasting lipids (total cholesterol, LDL-C, HDL-C, and triglycerides)
- the change from baseline in scores on the Impact of Weight on Quality of Life – Lite (IWQOL-Lite)[4,5]
- the change from baseline in scores on the Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function Short Form 10a (PROMIS SF 10a)
- the change from baseline in scores on the Eating-related Concept Questionnaire (ERCQ)

5.4.2. Analysis Methods

The analysis of exploratory endpoints will use the observed data through Week 12 while on treatment (up to the last dose of study drug plus 14 days). The analysis of glycemic parameters (e.g., HbA_{1c}, FPG, fasting insulin, HOMA-B, HOMA-IR) will be based on the measurements prior to rescue medication. The continuous exploratory efficacy endpoints (i.e., change from baseline in BMI, HbA_{1c}, FPG, HOMA-B, HOMA-IR, SBP, DBP, pulse rate, and rate pressure product) with more than one planned post-baseline timepoint will be analyzed using a MMRM model similar to the model used to analyze the primary efficacy endpoint based on the mITT analysis set. An analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline measurement as a covariate will be used for endpoints with only one planned post-baseline timepoint (e.g., waist circumference, fasting insulin, fasting C-peptide, total cholesterol, LDL-C, and HDL-C). 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 versus end of treatment.

The categorical exploratory efficacy endpoints will be analyzed using a logistic regression model similar to the model used to analyze the proportion of subjects with ≥5% weight loss.

An ANCOVA model with treatment as a fixed effect and baseline measurement as a covariate will be used to analyze the exploratory PRO endpoints. The additional PRO analyses will be described in a separate SAP.

6. SAFETY

All safety analyses and summaries will be based on the safety analysis set (Section 2.2.3). 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 double-blind treatment phase.

The evaluation of safety will be based on the incidence of adverse events, hypoglycemia episodes, and changes in clinical laboratory test results and vital sign results (blood pressure and 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. 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 (12-week) treatment phase plus 35 days. 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 (i.e., 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 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).[3] 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 a combined analysis 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 14 days for JNJ-64565111 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 12. 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 postbaseline clinically important laboratory values will be presented and 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 JNJ-64565111 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 and blood pressure (systolic and diastolic) will be summarized at each assessment time point. Changes from baseline will be summarized for the 12-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 12-week treatment phase. The descriptive statistics will be presented based on measurements on study medication, including up to a maximum of 14 days for JNJ-64565111 and placebo subjects, as well as all measurements regardless of the time of the last dose for subjects who discontinue from treatment before Week 12. The pulse and blood pressure measurements will be based on the average of the consecutive sitting pulse and blood pressure readings that were 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 JNJ-64565111 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, 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, all subjects will have 1 additional visit (Day 4 ± 1 day sampling window) to collect a non-trough PK sample. 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 16 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. ≥5% and ≥10% weight loss response rates and % weight loss at Week 12 will be presented in a bar graph by the corresponding serum JNJ-64565111 concentration quartiles at Week 12 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:

- Discontinued SC study agent administrations.
- Skipped a 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 12 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 6 sample – date of previous dose before date of Week 6 sample is < 3 days or > 11 days, then exclude Week 6 sample

- If relative Study Day of Week 12 sample is < Day 80 or >Day 88 then exclude Week 12 sample
- If relative Study Day of Week 16 sample is < Day 108 or >Day 116 then exclude Week 16 sample
- If subject discontinues treatment early, then exclude the "Week 16" 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 16 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 2, 6, 12, and 16) 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 12.
- ≥5% and ≥10% weight loss response rates and % weight loss at Week 12 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 6 and antibody to JNJ-64565111 status at Week 12 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

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2. Pinheiro J, Bornkamp B, Glimm E, Bretz, F. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014;33(10):1646-1661.
3. Crowe BJ 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.
4. 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.
5. 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 12/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
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

Laboratory Test	**Parameter for ANY value and LAST value**
	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 SPECIAL 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.