SYNOPSIS FOR CLINICAL REGISTRY

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-16269110 (formerly R256918)

Protocol No.: Protocol R256918OBE2001

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Dose-Ranging Study to Investigate the Safety and Efficacy of JNJ-16269110 in Overweight and Obese Subjects

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Publication (Reference): none

Study Period: 25 October 2007- 30 June 2008

Phase of Development: 2

Objectives: The primary objective of the study was to find appropriate, clinically relevant dosages (among the 5, 10, and 15 mg twice-daily dosages) of JNJ-16269110 by assessing mean changes in body weight compared to placebo. Secondary objectives were to estimate the dose-response relationship between the different dosages of JNJ-16269110 and the decrease in body weight, to estimate the effect on weight loss of different JNJ-16269110 dosages versus placebo as expressed by mean percent change from baseline in body weight and in body mass index (BMI), and the percentage of subjects who lost at least 5% or 10% of their initial body weight, to estimate changes in body composition using anthropometric measurements and by means of Dual X-Ray Absorptiometry (DEXA) to explore if weight loss was predominantly due to loss of fat mass, to explore changes in obesity-associated comorbidities as assessed by glucose homeostasis, fasting lipid profile, and systolic and diastolic blood pressure, to explore the effect of JNJ-16269110 on changes in levels of peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and oxyntomodulin, to explore the impact of health status using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) Questionnaire, to explore patient-reported assessment of gastrointestinal (GI) symptoms, to assess safety and tolerability with specific emphasis on GI adverse events, hepatic function, and absorption of lipid-soluble vitamins and essential fatty acids and to assess pharmacokinetic (PK) exposure.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study conducted at 18 sites in Europe. Approximately 320 overweight or obese subjects were to be randomized equally to 1 of 4 treatment arms during the double-blind phase of the study. Randomization was balanced by using randomly permuted blocks and was stratified by study center and a run-in weight loss of ≤2 kg or > 2 kg. Eligible subjects were men or women, aged 18 to 65 years, inclusive, with a stable weight, a BMI ≥30 kg/m^2 and <50 kg/m^2 or a BMI ≥27 kg/m^2 or <50 kg/m^2 in the presence of controlled hypertension and/or treated or untreated dyslipidemia. Subjects with an established diagnosis of diabetes mellitus were excluded from participation. Administration of study medication began on the first day of the double-blind phase. All study medications were administered in a twice-daily (bid) regimen in equally divided doses. An internal Data Monitoring Committee evaluated safety and efficacy data from the study at prespecified intervals. An interim analysis of safety and efficacy data was conducted when approximately the first 160 (ie, 50%) randomly assigned subjects (approximately 40 subjects in each treatment group) completed the study.

Number of Subjects (planned and analyzed): Approximately 320 overweight or obese subjects were to be randomized equally to 1 of 4 treatment arms during the double-blind phase of the study. A total of 321 subjects were randomized and 319 who received study medication were included in the Intent to Treat (ITT) analysis set. All subjects in the ITT analysis set were included in the safety data analyses and all

subjects in the ITT analysis set with both baseline and postbaseline efficacy data were included in the efficacy data analysis.

Diagnosis and Main Criteria for Inclusion: To be enrolled in the study, men and women must have been between 18 and 65 years of age, and must have been obese or overweight at screening. They must have maintained a stable weight in the 3 months before the start of the run-in period and must have had a BMI of ≥30 kg/m^2 and <50 kg/m^2 or ≥27 kg/m^2 and <50 kg/m^2 in the presence of controlled hypertension and/or treated or untreated dyslipidemia.

Test Product, Dose and Mode of Administration, Batch No.: Administration of study medication began on the first day of the double-blind phase. All study medications were administered in a bid regimen in equally divided doses, according to the following daily dosages:

Treatment Group	Dose	Regimen	Total Daily Dose
10 mg/day	5 mg	bid	10 mg
20 mg/day	10 mg	bid	20 mg
30 mg/day	15 mg	bid	30 mg

Study medication was administered orally with the meal, 1 capsule in the morning and 1 capsule in the evening. Batches of study medication and expiration dates are indicated in the table below.

Batches of Study Medication Used in the Study

Study Medication	Lot number	Expiration date
JNJ-16269110 5 mg	07G05/F026	July 2008
JNJ-16269110 10 mg	07G06/F027	July 2008
JNJ-16269110 15 mg	07G09/F028	July 2008
Placebo	07G04/F029	July 2008

Reference Therapy, Dose and Mode of Administration, Batch No.: NA

Duration of Treatment: The study was divided into 3 phases: a 5-week pretreatment phase (including a 1-week screening period and a 4-week run-in period), a 12-week double-blind phase during which study medication was administered, and a 2-week follow-up phase.

Criteria for Evaluation: Blood and urine samples for pharmacokinetics and pharmacodynamics and safety were collected at predefined timepoints, as specified in the Time and Events Schedule.

Efficacy: Efficacy was evaluated by assessing body weight and composition, comorbidities associated with obesity, such as carbohydrate and lipid metabolism parameters, systolic and diastolic blood pressure and PYY, GLP-1, and oxyntomodulin.

Safety: Safety and tolerability were evaluated via an assessment of adverse events monitored continuously throughout the study, and clinical laboratory tests, 12-lead ECGs, vital signs and physical examinations were evaluated at screening, baseline and at timepoints as specified in the Time and Events Schedule during the double-blind phase and end of study or early withdrawal.

Pharmacokinetics: Descriptive statistics were provided for the plasma concentrations of JNJ -16269110 and its metabolites, the acid metabolite and the N-dealkyl metabolite, in each treatment group. No formal statistical comparison of PK results among dosage groups was performed. Actual and dosage normalized plasma concentrations were graphically displayed as a function of time postdosing and as a function of treatment duration.

Pharmacogenomics: On Day 1, a 10 mL blood sample was collected from subjects who consented to the pharmacogenomic component of the study.

Statistical Methods: Sample size calculation was based on testing the null hypothesis of no difference in mean changes in body weight from baseline to Week 12 between subjects who received a JNJ-16269110 dosage and those who received placebo. If 64 subjects were randomly assigned to each of the 4 treatment groups, the study would have approximately 80% power (2-sided with 5% significance level) to detect a difference of ≥2.0 kg in mean change in body weight (SD ≤4.0, ratio of difference/SD=0.5) from baseline to Week 12 between the JNJ-6269110 dosage and placebo. If an assumed dropout rate of 20% for the last observation carried forward data was applied in the adjustment of the sample size for this study, a total of 320 subjects would be needed to be randomly assigned to the 4 treatment groups (i.e., 80 subjects per treatment group).

For each dosage, the null hypothesis for testing was that there was no difference in mean changes from baseline to Week 12 LOCF in body weight between the JNJ-16269110 dosage and placebo. The alternative hypothesis was that the mean changes were different. The Hochberg procedure was applied to test the 3 hypotheses of each of the 3 dosages versus placebo to control the family-wise Type I error rate.

An analysis of covariance (ANOVA) model, including treatment, run-in weight loss stratum (≤2 kg or >2 kg), and study center as factors, was applied in the analysis of the percent change in body weight at each time point.

The ANCOVA model, similar to the model used for body weight (with baseline BMI as the covariate), was applied in the analysis of the change in BMI from baseline at each time point.

The differences in least-squares means between each of the 3 active treatment dosages and placebo and their 2-sided 95% CIs were estimated using the ANCOVA model. Descriptive statistics were produced for the percent change in body weight, BMI, and change in BMI for each time point

All subjects who were exposed to study medication were evaluated for safety. Safety data were summarized using descriptive statistics for treatment-emergent adverse events reported during the study and for pretherapy to posttherapy changes in clinical laboratory test results, vital sign measurements, and physical examination findings.

RESULTS:

A total of 419 subjects were screened and 321 subjects were randomized to 4 treatment groups. Three hundred nineteen randomized subjects who took at least 1 dose of medication were included in the ITT analysis set. The 2 randomized subjects (04400117 and 04400125) who were excluded from the ITT analysis set were lost to follow-up after the randomization and did not receive study medication. A total of 265 subjects completed the treatment period while 56 subjects (17%) discontinued early. The most common reason for discontinuation was an adverse event (37 [12%]).

Subject Completion/Withdrawal Information
(Study R256918OBE2001)

	Placebo (N=76) n (%)	JNJ-16269110 5 mg bid (N=80) n (%)	JNJ-16269110 10 mg bid (N=86) n (%)	JNJ-16269110 15 mg bid (N=79) n (%)	Total (N=321) n (%)
Total no. subjects randomized	76 (100)	80 (100)	86 (100)	79 (100)	321 (100)
Completed	64 (84)	70 (88)	71 (83)	60 (76)	265 (83)
Withdrawn	12 (16)	10 (13)	15 (17)	19 (24)	56 (17)
Withdrawal of consent	2 (3)	2 (3)	2 (2)	0	6 (2)
Lost to follow-up	3 (4)	0	2 (2)	3 (4)	8 (2)
Adverse event	7 (9)	6 (8)	11 (13)	13 (16)	37 (12)
Initiation of excluded conmed	0	0	0	1 (1)	1 (<1)
Other	0	2 (3)	0	2 (3)	4 (1)

Key: N=total number of subjects; n=number of subjects in group; bid= twice daily
Note: Percentages calculated with the number of subjects in each group as denominator.

Demographic and baseline characteristics were consistent with the population described in the study inclusion/exclusion criteria. Demographic or baseline characteristics between the treatment groups were well balanced. The average age of the subjects enrolled in the study was 46.5 years (range, 18 to 65 years). The majority (80%) of subjects were females and white (96%). The average body weight at baseline was 102.1 kg and average BMI was 36.0, with 92% of subjects having a BMI ≥30.

Efficacy: All 319 subjects in the ITT analysis set were included in the efficacy data analysis. All 3 dose groups had statistically significantly greater body weight loss at Week 12 LOCF than the placebo group.

Primary Efficacy Analysis: Change From Baseline at Week 12 Last Observation Carried Forward in Body Weight
(Study R267918-OBE2001: Intent-to-Treat Analysis Set)

	Placebo (N=76)	JNJ-16269110 5 mg BID (N=80)	JNJ-16269110 10 mg BID (N=86)	JNJ-16269110 15 mg BID (N=77)
Body weight at baseline				
N	75	79	85	77
Mean (SD)	101.25 (18.071)	104.26 (16.673)	102.19 (14.274)	100.54 (18.585)
Body weight at week 12 LOCF				
N	75	79	85	77
Mean (SD)	99.64 (18.301)	101.06 (16.322)	97.98 (13.944)	95.46 (17.959)
Mean change from baseline	-1.61 (3.474)	-3.21 (3.687)	-4.21 (2.777)	-5.08 (4.038)
P-value(minus placebo) [a,b]		0.006	<0.001	<0.001
Diff. of LS Means (SE)		-1.51 (0.551)	-2.57 (0.540)	-3.51 (0.554)
95% CI		(-2.598; -0.428)	(-3.631; -1.505)	(-4.596; -2.414)

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, baseline body weight, and study center (type III SS).
[b] Pairwise comparison: P-values and CI associated with Fisher's LSD procedure.
Note: Subjects in the ITT analysis set with both baseline and post

.

There was a dose-related increase in the proportion of subjects who achieved a weight loss of at least 5% with a maximum in the 15 mg bid group of 48.1%. In this short-term study, the number of subjects achieving a weight loss of at least 10% was small.

Subjects in the JNJ-16269110 treatment groups had proportionally greater reductions compared to placebo in total body fat mass than in lean body mass . Mean change in total body fat mass (%) was -4.4, -8.0, -9.1, and -11.3 in the placebo, 5 mg bid, 10 mg bid, and 15 mg bid groups, respectively. No meaningful differences relative to placebo in mean change in total lean mass (%) was observed. Statistically significant changes in percent abdominal fat were observed in the 15 mg bid group. Loss of weight is predominantly loss of fat mass. The demographics of this subset of subjects were not different than the entire study population.

No significant differences were observed in hip and waist circumference, and in waist/hip ratio in any of the treatment groups.

In the active treatment groups, a dose-related decrease in LDL cholesterol was observed. In the highest dosing group, there was a small decrease in HDL cholesterol. Since the reduction in LDL-C was greater than the decrease in HDL-C, the LDL-C/HDL-C ratio decreased in all active treatment groups to a similar extent. A small decrease in median fasting triglycerides levels was observed in the placebo group, with small mean increases observed in the active treatment groups.

A decrease in ApoB100, as well as in ApoA1 was observed in the highest dosing group.

In this non-diabetic study population, there were no meaningful changes in glycemic control in any of the dose groups.

Dose-dependent and sustained decreases in both systolic and diastolic blood pressure were observed in the active treatment groups, whereas only minor changes occurred in the placebo group. These changes occurred early on-treatment, before significant weight loss had been achieved. In the small subset of subjects with baseline values higher than 130/80, a larger decrease in blood pressure was observed, compared to the overall study population. There were too few subjects with baseline values higher than 140/90 for a subgroup analysis.

Pharmacokinetics: Following bid oral administration of JNJ-16269110 at 5, 10, or 15 mg, plasma concentrations for each of the analytes increased proportionally with increases in dose. Steady-state concentrations were reached by Week 4 for JNJ-16269110 and the acid metabolite and by Week 8 for the N-dealkyl metabolite, and were maintained until the end of the study at Week 12.

PATIENT-REPORTED OUTCOMES RESULTS:

In general, IWQOL-Lite scores improved from baseline to week 12 with self-esteem and physical function scores improving the most. There were no clear dose related trends or consistent differences between groups, including placebo. No significant correlations were seen between IWQOL-Lite domain or Total scores and weight loss.

SAFETY RESULTS:

At least 1 adverse event was reported in 61 (80%) subjects in the placebo group, 75 (94%) subjects in the 5 mg bid group, 78 (91%) subjects in the 10 mg bid, and 75 (97%) subjects in the 15 mg bid group. The most commonly reported (those occurring in ≥10% of subjects in any treatment group) adverse events were diarrhea, nausea, upper abdominal pain, nasopharyngitis, headache, fatigue, vomiting, constipation, influenza, flatulence and frequent bowel movements. Adverse events of headache, constipation, and influenza were reported more frequently in the placebo treatment group, the other adverse events occurred more frequently in a JNJ-162699110 treatment group. The incidence of diarrhea, nausea, and upper abdominal pain in JNJ-16269110-treated subjects appeared to be dose-related.

No subjects died during the study. A total of 5 (2%) subjects in the JNJ-16269110 treatment groups (2, 2, and 1 subjects in the 5 mg bid, 10 mg bid, and 15 mg bid groups respectively) were reported to have serious adverse events during the study. No particular specific adverse event term was reported for more than one subject. None of these events were considered by the investigator to be related to study medication.

A total of 30 (12%) subjects in the JNJ-16269110 treatment groups had adverse events that resulted in discontinuation from the study. There was an apparent dose-related increasing incidence of adverse events, largely due to events in the GI SOC, leading to discontinuation. The adverse events that most frequently led to discontinuation were diarrhea and nausea. Most GI adverse events leading to discontinuation were considered by the investigator as being moderate to severe in intensity and related to study drug. Most of the discontinuations occurred in the first 3 weeks of the study.

Subjects in the JNJ-16269110 treated groups reported more bother from gastrointestinal symptoms compared to subjects in the placebo group. The symptoms most commonly reported as bothersome were loose or watery stools. The incidence of reported bother for all gastrointestinal symptoms decreased over time. Although subjects in the JNJ-16269110 treatment groups relative to the placebo group reported more bother from gastrointestinal symptoms, 61% (15 mg bid) to 67% (10 mg bid) of the subjects reported being very interested in taking the study medication again compared to 58% in the placebo group at Week 12.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Dose-related weight loss was observed with all 3 doses of JNJ-16269110 compared with placebo, without an apparent plateau reached at Week 12
- Dose-related GI adverse events were commonly observed, especially in the first 3 weeks of treatment, were generally mild-moderate in intensity, and decreased in frequency over the 12-week treatment period
- JNJ-16269110 was adequately tolerated and demonstrated an acceptable safety profile.

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