SYNOPSIS

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

Protocol No.: R256918OBE1008

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Effect of JNJ-16269110 on Hepatic Triglyceride Content in Obese Subjects

EudraCT Number: 2007-006175-36

NCT No.: NCT01041677

Clinical Registry No.: CR013735

Principal Investigator: Aila Rissanen, MD, Helsinki University Hospital, Finland **Study Center(s):** The study was conducted in 3 countries and had 4 sites: 1 site each in Sweden and Finland and 2 sites in The Netherlands.

Publication (Reference): Data from this study has not been published.

Study Period: 05 February 2008 to 06 October 2008; Database lock date: 15 April 2010.

Phase of Development: 2

Objectives:

The primary objective of the study was to assess mean changes in hepatic triglyceride content (HTGC) from baseline to Week 6 and 12 by ^{1}H Magnetic Resonance Spectroscopy (^{1}H-NMRS) in obese subjects treated with JNJ-16269110, 10-mg twice daily, 15 mg twice daily, or placebo twice daily

Secondary objectives were to:

- To investigate time-course, dose-dependency, and relationship of changes in HTGC to pharmacokinetic (PK) exposure
- To evaluate changes in HTGC versus observed changes in weight of JNJ-16269110 versus placebo
- To explore changes in obesity-associated co-morbidities as assessed by glucose homeostasis, fasting lipid profile, and systolic and diastolic blood pressure (BP)
- To explore the effect of JNJ-16269110 on 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 and hepatic function
- To assess PK exposure and to explore exposure-response relationships
- In a subset study of Finnish subjects, effects on subcutaneous fat tissue morphology and metabolism were evaluated; results will be described in a separate report

Methods:

- This was a randomized, double-blind, placebo-controlled, parallel-group study with 3 treatment groups, each consisting of 27 obese subjects
- Obese (BMI greater than or equal to 30 kg/m^2 and less than 50 kg/m^2) men or women aged 18 to 65 years, inclusive, with an HTGC between 3% and 15% and who met all other enrollment criteria were randomly assigned to receive either 10 mg of JNJ-16269110 twice daily, 15 mg of JNJ-16269110 twice daily, or placebo twice daily
- Subjects with a diagnosis of diabetes mellitus were excluded
- There was a 10-day screening period to confirm subject eligibility;
- NMRS screening was performed only if subjects were declared eligible after the general screening
- For the substudy (conducted at the site in Finland only), a separate informed consent form (ICF) was signed by the subjects; participation in the substudy was optional, and not contingent on their continuation in the main study
- A follow-up evaluation was performed 14 days (at approximately Week 14) after the end of treatment The total study duration for each subject was approximately 15 weeks
- In the substudy (conducted at the site in Finland only), fasting blood and adipose tissue samples were taken to assess blood parameters and signaling molecules related to fat tissue metabolism

Number of Subjects (planned and analyzed): The intent-to-treat (ITT) analysis set included all randomly assigned subjects who received study drug; the per protocol (PP) analysis set included all the subjects in ITT analysis sets who did not have major protocol violations. The primary analyses for both efficacy and safety data were based on the ITT analysis set.

Eighty-one subjects were planned (27 subjects in each of the 3 treatment groups) to be enrolled; 71 subjects were randomized in this study, and the ITT analysis set included 70 randomized subjects who received study drug.. There were 70 subjects in the ITT analysis set and safety analysis set; 69 in the PP analysis set, with 23 or 24 obese subjects in each treatment group.

Diagnosis and Main Criteria for Inclusion:

- Obese men or women between 18 and 65 years of age, inclusive, with a Body Mass Index (BMI) ≥30 kg/m2 and <50 kg/m2. with a stable weight (ie, any increase or decrease was not to be more than 5 kg in the 3 months before the screening period)
- An HTGC between 3% and 15% (by screening ^{1}H-NMRS)
- Fasting plasma glucose <7.0 mmol/L (126 mg/dL) at screening.
- If subjects were hypertensive, BP had to be well controlled with appropriate drug treatment.
- Subjects diagnosed with dyslipidemia as a result of screening assessments could have continued in the study if, in the clinical judgment of the investigator, initiation of lipid-lowering therapy was not required either immediately or during the course of the study
- Ability to enter the 60-cm diameter coil of the NMRS machine
- Not having any metal objects in the body or on the body that could not be removed (including pacemaker, prostheses, bullets, certain types of tattoos, piercings, metal based intrauterine devices, ferromagnetic surgical clips).
- No history of obesity with a known cause (eg, Cushing's disease).
- No established diagnosis of diabetes mellitus or treatment with glucose-lowering prescription drugs.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-16269110 was supplied as hard gelatin oral capsules filled with beads in the strengths of 10 mg (Lot No. 07G06/F027) and 15 mg (Lot No. 07G09/F028). The expiry date for all JNJ-16269110 study drug was July 2008.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as a matching capsule (Lot no. 07G04/F029). The expiry date was July 2008.

Duration of Treatment: The study consisted of a 12-week treatment period.

Criteria for Evaluation:

Efficacy Evaluations:

Efficacy was evaluated by assessing the following parameters:

Body weight, BMI, body composition (waist and hip circumference, waist/hip ratio), mean percent change in HTGC at Week 6 and Week 12 (or at end-of-treatment visit, defined as the final posbaseline visit in the double-blind treatment phase, in case of early withdrawal), comorbidities associated with obesity: (a) carbohydrate metabolism parameters (ie, fasting plasma glucose and serum insulin, with calculation of insulin sensitivity and beta-cell function by means of homeostatic model assessment-2, hemoglobin A_{1c} [HbA_{1c}]); (b) lipid metabolism parameters (ie, triglycerides, total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], very low density lipoprotein [VLDL], total/HDL ratio, LDL/HDL-C ratio, apolipoprotein B [ApoB], apolipoprotein A1 [ApoA1], lipoprotein (a), and detailed nuclear magnetic resonance spectroscopy (NMRS) lipoprofile test; systolic and diastolic BP, and IWQOL-Lite).

Pharmacokinetic Evaluations:

Predose fasting venous blood samples of 6 mL were collected for determination of JNJ-16269110 concentrations at Week 4, 6, 8, and Week 12. Concentrations of JNJ-16269110 were determined using a validated liquid chromatography-tandem mass spectrometry method. Remaining plasma was used to determine the concentrations of metabolites or the R-enantiomer using a qualified research method.

Pharmacogenomic Evaluations:

A 10-mL blood sample was collected from subjects who provided consent and opted to participate in the pharmacogenomic component of the study in Week 2 of the treatment period. Statistical evaluation of genotyping data will be performed in an exploratory manner only and reported separately from this Clinical Study Report.

Safety Evaluations:

The study included the following evaluations of safety and tolerability:

Monitoring of adverse events, clinical laboratory tests including serum beta-human chorionic gonadotropin and urine pregnancy testing, electrocardiograms (ECGs), vital sign measurements (pulse and BP), physical examination, and patient reported assessment of GI symptoms.

Special clinical laboratory tests for the assessment of safety were as follows: (a) coagulation status: international normalized ratio (INR), activated partial thromboplastin time (aPTT); (b)essential fatty acid status (linoleic acid and α-linolenic acid); (c) lipid-soluble vitamin status: vitamin A (retinol, beta-carotene), vitamin D (25-hydroxy-cholecalciferol), vitamin E (alpha-tocopherol), vitamin K, vitamin A/total cholesterol ratio, vitamin E/total cholesterol ratio; (d) liver function tests (LFTs): alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and alkaline phosphatase; total and direct bilirubin, and samples for analysis of ALT isoforms were also collected.

Statistical Methods:

The sample size was estimated on the basis of the extent of weight loss after 12 weeks of treatment with JNJ-16269110 is not known, nor has the effect of JNJ-16269110 on HTGC been previously evaluated. It is expected that HTGC would decrease in the active treatment groups due to weight loss, with the assumption that JNJ-16269110 does not directly increase HTGC given the intestinal-selective MTP inhibition. It is therefore expected that observed changes in HTGC will be commensurate with the degree of weight loss. It was estimated that group sample sizes of 23 would achieve 80% power to detect a mean difference in HTGC of 0.63% with group standard deviations (SD) of 0.48% and 0.96% and with a significance level (alpha) of 0.05 using a 2-sided 2-sample t-test. In order to cover for about 20% possible early withdrawal of subjects during the 12-week study it was proposed to recruit 27 subjects in each treatment group, ie, 81 in total.

Descriptive statistical summaries were produced for all the efficacy variables. For the primary efficacy variable, change from baseline for HTGC (%), the mixed-effects model analysis to evaluate the effect of treatment over time (on the ITT and PP analysis sets) was applied. This model included treatment, time, and study center as fixed effects, and subject as the random effect. The baseline value of HTGC was included as covariate. The comparison in least square mean (LSM) between each of the two active treatment doses and placebo at 12 weeks was performed using this model. There was no imputation of missing data in the mixed effects model analysis (Mixed Models for Repeated Measures). As this was not a confirmatory study no multiplicity adjustment was adopted.

For sensitivity purposes an analysis of covariance (ANCOVA) model based on the last (postbaseline) observation carried forward (LOCF) method and an analysis of complete cases were performed. In the LOCF approach a missing Week 12 HTGC value was replaced by a Week 6 HTGC value. Only subjects with at least 1 postbaseline measurement were included in the analysis. The model included treatment and center as factors and baseline HTGC as covariate.

Based on the primary efficacy variable, the proportion of subjects (number and percent who reached a value of HTGC (%) ≤5% or > 5% at Week 12 and at End of Treatment were tabulated.

Adverse events and GI-related adverse events were summarized. Descriptive statistics and change from baseline were calculated for vital sign measurements, 12-lead ECGs and clinical laboratory analyte values.

Data Monitoring Committee (DMC): A company-internal DMC, independent from the study team, monitored the progress of the study so as to assure early detection and appropriate action for any important safety signal. If during review of the safety data, the DMC observed that any of the safety data pointed towards distinctive, unfavorable safety or tolerability results for any particular group, it could have advised that the study design to be modified or the study halted.

Interim Safety and Efficacy Analysis: An interim analysis was carried out by a study- independent DMC according to a DMC charter so as to provide an early assessment of safety and efficacy. The interim analysis results were not disclosed to anyone directly involved in the execution of the study to avoid the introduction of bias. The study was not to be terminated based on the results of the interim efficacy analysis (unless a safety issue was observed requiring such an action), so no statistical penalty (ie, reduction in final alpha) was instituted. Summary statistics, including the point and interval estimates and a graphical evaluation of the data, were performed by treatment group, and with the treatment groups identified .

RESULTS:

Four sites in 3 countries (Sweden, Finland, and The Netherlands) recruited subjects for this study. There were 263 subjects screened, with 192 screen failures; a total of 71 subjects were randomized, 23 to the placebo group, 24 to the 10-mg JNJ-16269110 twice-daily group, and 24 to the 15-mg JNJ-16269110 twice-daily group. Sixty subjects (85%) completed the study. Eleven subjects discontinued early from the study: (4 [6%] withdrew consent, 4 [6%] due to an adverse event and 3 [4%] for other reasons). Recruitment for the study was severely hampered by a high screening failure rate (HTGC <3%) and Based on the interim analysis, the DMC endorsed the clinical team's proposal to stop recruitment early in order to allow timely reporting of the final results..

The study completion withdrawal information is presented in the table below:

Study Completion/Withdrawal Information
(Study R256918OBE1008: All Randomized Subjects Analysis Set)

Standardized Disposition Term	Placebo (N=23) n (%)	JNJ-16269110 10-mg bid (N=24) n (%)	JNJ-16269110 15-mg bid (N=24) n (%)	Total (N=71) n (%)
Completed	22 (96)	18 (75)	20 (83)	60 (85)
Withdrawn	1 (4)	6 (25)	4 (17)	11 (15)
Withdrawal of consent	0	1 (4)	3 (13)	4 (6)
Adverse event	0	4 (17)	0	4 (6)
Other	1 (4)	1 (4)	1 (4)	3 (4)

Bid = twice daily; n = size of sub sample; N = total sample size
Note: Percentages calculated with the number of subjects in each group as denominator.

The demographic and baseline characteristics for the 3 treatment groups were consistent with the inclusion and exclusion criteria described in the protocol. A summary of the demographic and baseline characteristics is presented in the table below.

Demographic and Baseline Characteristics
(Study R256918OBE1008: ITT Analysis Set)

	Placebo (N=23)	JNJ-16269110 10-mg bid (N=24)	JNJ-16269110 15-mg bid (N=23)	Total (N=70)
Age (years)				
Mean (SD)	47.8 (8.50)	48.3 (11.98)	49.8 (11.27)	48.6 (10.59)
Median	50.0	48.5	51.0	50.0
Range	(30;61)	(22;65)	(21;63)	(21;65)
Age group, n (%)				
18-29	0	2 (8)	2 (9)	4 (6)
30-49	11 (48)	11 (46)	6 (26)	28 (40)
50-65	12 (52)	9 (38)	15 (65)	36 (51)
≥65	0	2 (8)	0	2 (3)
Sex, n (%)				
M	10 (43)	9 (38)	5 (22)	24 (34)
F	13 (57)	15 (63)	18 (78)	46 (66)
Race, n (%)				
White	22 (96)	24 (100)	23 (100)	69 (99)
Asian	1 (4)	0	0	1 (1)
Baseline weight (kg)				
Mean (SD)	105.6 (16.09)	104.2 (11.44)	96.9 (17.22)	102.3 (15.33)
Median	101.5	104.0	95.0	100.7
Range	(73;130)	(82;127)	(79;151)	(73;151)
Baseline height (cm)				
Mean (SD)	170.9 (10.69)	171.1 (9.30)	167.3 (11.84)	169.8 (10.63)
Median	170.0	171.5	165.0	169.0
Range	(150;189)	(152;190)	(153;194)	(150;194)
Baseline BMI (kg/m^2)				
Mean (SD)	36.0 (3.42)	35.7 (3.72)	34.4 (2.47)	35.4 (3.28)
Median	35.5	35.9	34.0	35.0
Range	(32;45)	(30;44)	(31;40)	(30;45)
Baseline HTGC (%)				
Mean (SD)	6.520 (2.9972)	7.746 (4.1998)	6.269 (3.1124)	6.858 (3.5015)
Median	5.900	6.205	5.380	5.700
Range	(3.03;13.01)	(3.26;19.37)	(2.95;13.09)	(2.95;19.37)
Baseline HTGC group, n (%)				
≤5%	10 (43)	10 (42)	10 (43)	30 (43)
>5%	13 (57)	14 (58)	13 (57)	40 (57)

Bid = twice daily; BMI = body mass index; HTGC = hepatic triglyceride content; ITT = intent-to-treat; N = total sample size
SD = standard deviation

EFFICACY RESULTS

- A mean decrease from baseline in HTGC was seen for all treatment groups (ITT analysis set) throughout the treatment period with the largest mean decrease seen for the 15 mg JNJ-16269110 twice daily group.
- For the primary mixed-model analysis (mixed model in the ITT analysis set), the changes in HTGC in the active JNJ 16269110 treatment groups did not reach statistical significance compared with the placebo group.
- Statistically significant decreases in body weight in the 10- and 15-mg JNJ-16269110 twice-daily groups compared with placebo were observed.
- A numerically higher proportion of subjects in the 15-mg JNJ-16269110 twice-daily group had an HTGC reduction of ≥50% compared with the 10-mg JNJ-16269110 twice-daily and

the placebo. A relative reduction in HTGC of at least 50% was obtained in 68% of the subjects in the 15 mg JNJ 16269110 twice-daily group compared with approximately 39% of the subjects in the 10 mg JNJ 16269110 twice-daily group and 38% of the subjects in the placebo group.

- The data for all treatment groups suggest that a mean weight loss of 8% corresponds with a mean relative decrease of 55% in HTGC.
- A trend towards dose-dependent mean decreases from baseline in total cholesterol, LDL-C, and ApoB, were observed at Week 6 and end of treatment.
- At Week 12 and end of treatment, no significant changes were observed in baseline in fasting plasma glucose, fasting serum insulin and in HbA1C across treatment groups.
- A trend for dose-related decreases from baseline in systolic and diastolic BP was observed early during the study and continued until Week 12.These changes were observed at the first on-treatment visit, before significant weight loss was observed. At Week 12, there were significant difference in systolic BP observed between the 15-mg JNJ-16269110 twice-daily and placebo group.
- A decrease in pulse was observed in all treatment groups including placebo with no clinically significant differences between the active treatment groups and the placebo group.
- In general, IWQOL-Lite scores improved from baseline to Week 12 with physical function and self-esteem scores improving the most. There were no clear dose-related trends or differences between treatment groups, including the placebo group.

PHARMACOKINETIC RESULTS:

Seventy subjects participated in the PK assessments in this study. Plasma concentrations for JNJ-16269110 increased dose proportionally following twice-daily administration of JNJ-16269110 at 10 or 15 mg twice daily, and steady-state concentrations were maintained over the PK sampling period (between Week 4 and Week 12).

PHARMACOGENOMIC RESULTS:

The results of pharmacogenetic analyses performed as part of this study are not included in this report, and will be reported separately.

SAFETY RESULTS:

- There were no deaths, serious or severe adverse events reported in this study.
- Treatment-emergent adverse event was reported in 21 (91%) subjects in the placebo group, 23 (96%) of subjects in the 10-mg JNJ-16269110 twice-daily group, and 21 (91%) of subjects in the 15-mg JNJ-16269110 twice-daily group.
- There was a higher incidence of diarrhea, frequent bowel movements and constipation in the JNJ-16269110 treatment groups.
- The most commonly-reported (ie, those occurring in ≥10% of subjects treated with JNJ-16269110) adverse events were diarrhea, nasopharyngitis, headache, nausea, abdominal pain upper, constipation, and dyspepsia. In general, there was a higher incidence of gastrointestinal adverse events in the JNJ-16269110 treatment groups. In general, there was a higher incidence of GI adverse events in the JNJ-16269110 treatment groups.
- The majority of adverse events outside of the GI system organ class were considered by the investigator as either not related or doubtfully related to study drug, whereas most adverse events in the GI system organ class were considered as possibly or probably related to study drug across all the treatment groups (including placebo). A total of 2 adverse events, diarrhea and fecal incontinence, both occurring in 1 subject from the 10-mg JNJ-16269110 twice-daily group, were considered very likely related to study drug.
- Four subjects, all from the 10-mg twice-daily group, had adverse events that led to discontinuation from the study. These events were diarrhea, malaise, abdominal distension,

abdominal pain upper, faecal incontinence, nausea, eructation, dizziness, dyspepsia, anorexia, pain in extremity, headache, and pollakiuria.

- Subjects in the JNJ-16269110 treatment groups reported more bother from gastrointestinal symptoms compared with subjects in the placebo group. The symptoms most commonly reported as bothersome were loose or watery stools.
- There were no clinically relevant changes from baseline in mean hematology, clinical chemistry or urinalysis, with the exception of the following: Mean values for linoleic acid decreased for all 3 treatment groups throughout the double-blind treatment period. This decrease was more significantly noted in the JNJ-16269110 groups.
- There were no incidences of increase in ALT or AST ≥3 times the ULN or of total bilirubin. One subject in the 15-mg JNJ-16269110 group had alkaline phosphatase levels of ≥1.5 times the ULN. No subjects met Hy's High Risk criteria at any point during the study.
- Four subjects, 2 from the placebo group, 1 from the 10-mg twice-daily group, and 1 from the 15-mg twice daily group, had abnormal laboratory values that were reported as adverse events.
  - One subject from the placebo group was reported with elevated creatine kinase (CK), elevated GGT, and elevated ALT;
  - One subject from the placebo group, was reported with mild blood CK increased;
  - One subject from the 10-mg twice-daily group was reported with of high density lipoprotein decreased, and blood TSH decreased; and
  - One subject from the 15-mg twice-daily group was reported with mild blood alkaline phosphatase increased.
- There were no consistent vital signs or ECG-related abnormalities observed in any of the 3 treatment groups.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- In general, a significant decrease in HTGC from baseline to Week 6 and Week 12 was observed in obese subjects treated with 10 and 15 mg JNJ-16269110 twice daily. For the primary mixed-model analysis in the ITT analysis set, the changes in HTGC in the active JNJ-16269110 treatment groups did not reach statistical significance compared with the placebo group. The data for all treatment groups suggest that a mean weight loss of 8% corresponds with a mean relative decrease of 55% in HTGC.
- Plasma concentrations for JNJ-16269110 increased dose-proportionally between 10-and 15-mg twice-daily, and steady-state concentrations were maintained over the PK sampling period (between Week 4 and Week12).
- Overall, JNJ-16269110 at doses of 10 and 15 mg twice daily demonstrated an acceptable safety profile in obese patients and was adequately tolerated. Dose-related GI adverse events were commonly observed and were generally mild to moderate in intensity.
- There were no new clinically significant safety signals that would preclude further clinical development of this compound.

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