SYNOPSIS

Issue Date: 20 April 2010
Document No.: EDMS-PSDB-8607608: 2.0

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.: R256918-DIA2001

Title of Study: A 12-Week, Double-Blind, Randomized, Placebo-Controlled Study in Type 2 Diabetes Mellitus Subjects to Evaluate the Efficacy, Safety and Tolerability of MTP Inhibitor JNJ-16269110

EudraCT Number: 2007-000031-26

Coordinating Investigator: Prof Kaj Stenlof, MD - SU/Sahlgrenska University Hospital, [redacted]; Sweden

Study Center(s): Subjects were screened at 68 centers in 11 countries: Belgium (1 site), Denmark (2 sites), Norway (2 sites), Finland (5 sites), Germany (7 sites), India (7 sites), the Netherlands (7 sites), Russia (7 sites), Sweden (7 sites), the United Kingdom (11 sites), and Poland (12 sites).

Publication (Reference): None

Study Period: The first subject was enrolled on 13 November 2007 and the date of the last observation for the last subject was 12 September 2008; database lock was on 15 October 2008.

Phase of Development: 2

Objectives: The primary objective of this study was to evaluate the effects of 12 weeks treatment with JNJ-16269110 on glycated hemoglobin A_{1c} (HbA_{1c}) concentration in subjects with Type 2 diabetes mellitus (T2DM). Additional key objectives included evaluation of the effects of 12 weeks treatment with JNJ-16269110 on: fasting plasma glucose and glycemic excursions and insulin secretion measured after a standardized, in-clinic mixed meal tolerance test (MMTT) for approximately 120 subjects participating in selected countries; fasting concentrations and postprandial responses of the gastrointestinal and pancreatic hormones to the standardized mixed meal; homeostasis model assessment (HOMA-2) estimates of insulin sensitivity (HOMA-2-%S) and beta cell function (HOMA-2-%R), based on plasma glucose, insulin and C-peptide responses to the MMTT; body weight, body mass index (BMI) and waist to hip ratio; fasting plasma lipids and postprandial triglyceride (PPTG) excursion after MMTT; blood pressure; safety and tolerability; and pharmacokinetic (PK) exposure of JNJ-16269110 to explore plasma exposure-response relationships and to develop a population PK model; and to evaluate quality of life and overall satisfaction with the study drug.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, international Phase 2a/b study involving subjects with T2DM who were on monotherapy with metformin. Subjects were randomized to 1 of 4 treatment groups (approximately 80 subjects per group), and received either 5 mg JNJ-16269110, 10 mg JNJ-16269110, 15 mg JNJ-16269110, or placebo twice daily (bid) for a period of 12 weeks.

The study consisted of a 28-day screening period, a baseline visit (Day –1), the treatment period (Days 1 to 84) and a follow-up visit (scheduled 10 to 14 days after the last dose of study drug administration). The overall duration of the study for each subject was approximately 18 weeks. Subjects were randomly assigned to a treatment group on Day -1 (baseline) and evaluated for baseline safety, PK, and efficacy assessments. In a subpopulation of approximately 120 subjects, (all randomized subjects in selected participating countries), a mixed meal tolerance test (MMTT) were performed, which included a standard meal and a 3-hour blood collection for glucose, insulin, C-peptide, triglycerides, and gastrointestinal

hormones (glucagon-like peptide [GLP-1] and peptide tyrosine tyrosine [PYY]).. During the treatment period, subjects visited the study center every 2 weeks (Week 2 to Week 12). At the follow-up visit, safety evaluations such as hematology, clinical biochemistry, urinalysis, vital signs, and ECG, physical examinations, and body weight measurements were repeated.

During the entire study, subjects continued to take metformin in the same dose and according to the same dosing regimen as before the study. Subjects were to carry on their usual daily physical exercise, and keep the diet as prescribed by the dietician, refraining from high fat food. However, if subjects met the predefined rescue criteria, metformin daily dose may have been increased or rescue medication given.

The original protocol was issued on 27 July 2007, and there were 2 international protocol amendments, Amendment INT-1 (dated 4 October 2007) and Amendment INT-2 (dated 27 March 2008). There were 3 local amendments to the protocol GER-1 (substantial), DEN-1 (non-substantial), and RUS-1 (non-substantial).

Number of Subjects (planned and analyzed): A minimum of 80 subjects were planned per treatment group (320 subjects total). A total of 352 subjects were randomly assigned to treatment (88, 84, 91, and 89 in the placebo and 5-, 10-, and 15- mg JNJ-16269110 treatment groups, respectively); 351 subjects were included in both the Intent-to-Treat (ITT) and safety analysis sets, 334 in the Per Protocol analysis set, and 94 (subjects from Sweden, Norway, and the Netherlands) were included in the MMTT analysis set.

Diagnosis and Main Criteria for Inclusion: Men and women, ages 18 to 70 years, who had a history of T2DM that was controlled with a stable daily dose of metformin for at least 2 months prior to screening. Fasting plasma glucose were to be less than 240 mg/dL (13.3 mmol/L) at the screening and baseline visits. Subjects had a BMI of at least 25 kg/m^2 and at most 45 kg/m^2, inclusive, and HbA_{1c} levels ≥7% and ≤10%.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-16269110 was provided as hard gelatin oral capsules of size DBAA filled with beads in the following strengths: 5 mg (lot number 07G05/F026), 10 mg (lot number 07G06/F027), and 15 mg (lot number 07G09/F028). The initial expiry date of the study drug was 31 July 2008 and the new expiry date after shelf life extension to 18 months was 31 January 2009.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was provided as matching capsules (lot number 07G04/F029).

Duration of Treatment: In all groups, JNJ-16269110 (5, 10, or 15 mg) or placebo was administered in the morning and in the evening with the meal (not on an empty stomach) for 12 weeks. The overall duration of the study for each subject was approximately 18 weeks.

Criteria for Evaluation:

Efficacy Evaluations: Efficacy was evaluated in all subjects by assessing: HbA_{1c}; carbohydrate metabolism parameters (ie, fasting plasma glucose and insulin and glucagon, HOMA-2-%S and HOMA-2-%B, and SMBG [including self-monitored fasting plasma glucose and 7-point glucose profiles]); lipid metabolism parameters; body weight, waist and hip circumference, and waist hip ratio; blood pressure; and patient reported outcome questionnaires. Plasma glucose, insulin, and C-peptide to assess insulin sensitivity and beta cell function were evaluated in a subset of 94 subjects (MMTT subset). Mechanistic exploration of PYY and GLP 1 in the fasting and postprandial states was also evaluated in the MMTT subset.

Pharmacokinetic Evaluations: Venous blood samples (3 mL) for the analysis of JNJ-16269110 concentration were collected before the morning dose of metformin, JNJ-16269110, or placebo at Weeks 4, 8, and 12 for all subjects. Only for subjects participating in the MMTT analysis, additional blood samples were taken at Week 12, 1.5 and 3 hours after administration of study drug during Week 12.

Pharmacogenomic Evaluations: Where local regulations permitted, a 10 mL blood sample was collected from subjects who consented to the pharmacogenomic component of the study. Participation in the DNA testing component of the study was voluntary and required separate informed consent.

Safety Evaluations: All safety assessments were performed starting from the Screening visit to the Follow-up visit and involved adverse events reporting, as well as hematology and clinical laboratory tests (including serum beta-human chorionic gonadotropin and urine pregnancy testing), urinalysis, physical examinations, vital signs, 12-lead electrocardiograms (ECGs).

In addition, several special clinical laboratory tests were performed for the assessment of other safety parameters, including assessment of lipid soluble vitamins and liver function tests (LFTs).

Statistical Methods:

The proposed sample size of 64 subjects per treatment group allowed detection of a difference of 0.5% HbA_{1c} for change from baseline between placebo and JNJ-16269110 with 80% power and a 2-sided 0.05 significance level. However, to allow for an anticipated dropout of 20%, 80 subjects were recruited per treatment group. Based on the literature, the standard deviation for change from baseline for the placebo and active treatment groups was expected to be 1.0%.

The ITT analysis set included the ITT subjects (ie, all randomized subjects who received at least 1 dose of study drug) and had at least 1 postbaseline measurement. All subjects in the ITT analysis set were included in the efficacy data analysis (with the exception of the MMTT analysis). The Per Protocol analysis set included all subjects from the ITT analysis set who did not have a major protocol violation. The MMTT analysis set included all randomized subjects in Sweden, Norway, and the Netherlands who received at least 1 dose of study drug and had at least 1 postbaseline MMTT measurement.

The primary efficacy variable was change in HbA_{1c} from baseline to Week 12; for the primary analysis, mixed model for repeated measurements (MMRM) analysis was used. The primary efficacy analysis included 3 pairwise comparisons between each of the 3 JNJ-16269110 doses (ie, 5, 10 and 15 mg twice daily) and placebo in mean change from baseline in HbA_{1c} at Week 12. The Hochberg procedure was applied for these comparisons to preserve the family-wise Type I error rate (α) at 5%. A repeated measurement analysis of change from baseline for HbA_{1c} was performed using a mixed-effects model to evaluate the effect of treatment over time. The primary efficacy analysis was also performed by metformin group (ie, <1,500 mg/day and ≥1,500 mg/day) as prespecified. The proportion of subjects who responded (ie, who reached a value of HbA_{1c} <7% and HbA_{1c} <6.5%) were tabulated.

Descriptive statistical summaries were produced for all secondary efficacy and other exploratory efficacy variables.

Treatment emergent adverse events, laboratory analyte values, vital sign measurements, and ECG data reported during the study were summarized. The safety analysis and summaries were based on the safety analysis set. No hypothesis testing was done for safety data.

RESULTS:

STUDY POPULATION:

A total of 652 subjects were screened at 68 centers in 11 countries. Two subjects who failed screening were randomized in error, but were withdrawn from the study without having taken any study drug. These subjects were not included in the Randomized Subjects Analysis Set, which consisted of 352 subjects. Three hundred and seven subjects (87%) successfully completed the study (Table 1). Forty-five (13%) subjects discontinued early; the most common reason for discontinuation was due to an adverse event. A higher percentage of subjects in the 10-mg bid and 15-mg JNJ-16269110 bid groups (13% and 9%, respectively) discontinued due to adverse events than in the placebo (5%) or 5-mg JNJ-16269110 groups (2%).

Table 1: Study Completion/Withdrawal Information
(Study R256918DIA2001: All Randomized Analysis Set)

	Placebo (N=88) n (%)	JNJ-16269110 5 mg bid (N=84) n (%)	JNJ-16269110 10 mg bid (N=91) n (%)	JNJ-16269110 15 mg bid (N=89) n (%)	Total (N=352) n (%)
Total no. randomized	88 (100)	84 (100)	91 (100)	89 (100)	352 (100)
Completed	77 (88)	78 (93)	75 (82)	77 (87)	307 (87)
Withdrawn	11 (13)	6 (7)	16 (18)	12 (13)	45 (13)
Withdrawal of consent	2 (2)	0	2 (2)	3 (3)	7 (2)
Lost to follow-up	1 (1)	1 (1)	0	0	2 (1)
Adverse event	4 (5)	2 (2)	12 (13)	8 (9)	26 (7)
Other	4 (5)	3 (4)	2 (2)	1 (1)	10 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.

The majority of subjects were white (86%) and most (63%) were 50 to 65 years old; a comparable number of men (54%) and women (46%) participated. The mean body weight at baseline was 94.9 kg, and the average BMI was 32.8 kg/m^2, with 70% of subjects meeting the standard definition for obesity (BMI >30 kg/m^2). The average HbA_{1c} at baseline was 7.83%. Demographic and baseline characteristics in the ITT analysis set were similar across the treatment groups. Seventy percent of subjects in all the treatment groups were receiving at least 1,500 mg of metformin per day.

Major protocol deviations were seen in 17 (5%) subjects and included subjects with a compliance rate of less than 80%, as far as the study medication intake was concerned, or subjects who entered the study although major entry criteria were not met, or subjects who received concomitant medication that was not allowed per the protocol.

A total of 351 subjects received at least 1 dose of study drug, and were included in the ITT analysis set. Most subjects (76%) received study treatment for 81 to 90 days. . b

EFFICACY RESULTS:

The primary efficacy variable was change in percent HbA_{1c} from baseline to Week 12; relatively small, but statistically significant, decreases from baseline at Week 12 in percent HbA_{1c} compared with placebo were seen for all 3 JNJ-16269110 dose groups, with the largest mean decreases seen for the 10- and 15-mg dose groups (Table 2).

Table 2: Primary Efficacy Analysis: Change From Baseline at Week 12 of HbA_{1c} (MMRM Analysis) - Intent-to-Treat Analysis Set
(Study R256918DIA2001: Intent-to-Treat Analysis Set)

	HbA_{1c} Value (%)					
	Baseline			Week 12		
Treatment	N	Mean	SD	N	Mean	SD
Placebo	88	7.97	0.918	78	7.68	1.014
JNJ-16269110 5 mg bid	83	7.74	0.777	76	7.35	0.694
JNJ-16269110 10 mg bid	88	7.75	0.643	74	7.23	0.836
JNJ-16269110 15 mg bid	89	7.85	0.760	75	7.32	0.862

	Change from Baseline Value						
Treatment	Mean	SD	LSMean (SE)	LSMean Difference[c]	95% Confidence Interval on Difference [a,b]		p value [a,b]
Placebo	-0.30	0.853	-0.27 (0.058)				
JNJ-16269110 5 mg bid	-0.39	0.658	-0.46 (0.058)	-0.19	(-0.34;	-0.04)	0.0150
JNJ-16269110 10 mg bid	-0.53	0.622	-0.55 (0.058)	-0.28	(-0.44;	-0.13)	0.0003
JNJ-16269110 15 mg bid	-0.54	0.686	-0.54 (0.058)	-0.28	(-0.43;	-0.12)	0.0004

Subjects in the ITT analysis set have a baseline and at least 1 post-baseline measurement.
[a] Test for no difference between treatment from a mixed model with treatment, baseline HbA_{1c}, day, country and treatment by day interaction as factors.
[b] Pairwise comparison: p values and CI from the LSMEANS of the above model.
[c] LS Mean on Difference Treatment compared to Placebo

Results of major secondary efficacy analyses were:

- A progressive reduction in fasting plasma glucose was observed through Week 8 across dose groups with generally stable subsequent fasting plasma glucose change from baseline from Week 8 through Week 12 in the ITT analysis set.
- Fasting LDL-C levels decreased significantly in the 15-mg JNJ-16269110 bid treatment group, whereas they increased modestly in the 5- and 10-mg JNJ-16269110 bid treatment groups; minimal change was observed in the placebo group. Fasting HDL-C levels increased modestly in the 5-mg and10-mg JNJ-16269110 bid groups, as well as the placebo group, whereas minimal change was observed in the 15-mg JNJ-16269110 group. Fasting triglyceride levels increased in all 3 JNJ-16269110 treatment groups in a non-dose dependent fashion and to a similar extent compared with placebo.
- Small decreases in SBP and DBP from baseline were seen at Week 12 across the placebo and active JNJ-16269110 treatment groups. Somewhat greater decreases were observed in subjects treated with 15 mg JNJ-16269110 bid compared with placebo and 5 or 10 mg JNJ-16269110 bid.
- For the 10-mg and 15-mg JNJ-16269110 bid treatment groups, a larger mean decrease in weight was observed than for the placebo or 5-mg JNJ-16269110 bid groups. The weight loss in subjects treated with 10-mg JNJ-16269110 and 15-mg JNJ-16269110 was significantly greater than in subjects treated with placebo ($p<0.0001$). The mean percent change in body weight from baseline to follow-up were -2.3%, -2.1%, -2.9%, and -3.8% in the placebo, 5-mg, 10-mg, and 15-mg JNJ-16269110 bid groups, respectively.

Results of other secondary efficacy analyses were:

- Median fasting insulin decreases were observed in the 10-mg and 15-mg JNJ-16269110 bid dose groups. These changes were not associated with similar changes in median fasting C-peptide levels. Slightly increased fasting glucagon concentrations were observed in the 15-mg JNJ-16269110 bid group.
- Modest and similar increases in insulin resistance, insulin sensitivity (HOMA-2-%S), and beta-cell function (HOMA-2-%B) assessments for the ITT analysis set were observed in all 3 JNJ-16269110 bid groups, as well as the placebo group.

PHARMACOKINETIC RESULTS:

Following bid oral administration of JNJ-16269110 at 5, 10, or 15 mg, plasma concentrations for JNJ-16269110 and its major metabolites, acid metabolite JNJ-16213119 and N-dealkylmetabolite JNJ-2775188 (both inactive), increased proportionally with increases in dose. The plasma concentrations of R-enantiomer JNJ-16202979 in most subjects at the 5 and 10 mg bid doses were below the quantitation limit; therefore, the dose-proportionality of this analyte could not be evaluated. Steady-state concentrations were reached by Week 4 for JNJ-16269110 and JNJ-16213119 and by Week 8 for JNJ-2775188, and were maintained until the end of the study at Week 12.

SAFETY RESULTS:

Overall, at least 1 adverse event was reported in 224 (64%) of subjects in this study (Table 3). There were no deaths. Five (1%) subjects had a serious adverse event during the study. A total of 26 (7%) subjects had adverse events that resulted in discontinuation from the study. Diarrhea was the most frequently reported adverse event resulting in discontinuation: 8 (9%) subjects in the 10-mg and 7 (8%) subjects in the 15-mg JNJ-16269110 bid group.

Table 3: Subjects With Serious Adverse Events/Reactions, Deaths, and Adverse Events/Reactions Resulting in Discontinuation (Study R256918DIA2001: Safety Analysis Set)

		JNJ-16269110			
	Placebo (N=88) n (%)	5 mg bid (N=84) n (%)	10 mg bid (N=90) n (%)	15 mg bid (N=89) n (%)	Total (N=351) n (%)
One or more serious adverse events	1 (1)	2 (2)	2 (2)	0	5 (1)
Deaths	0	0	0	0	0
Adverse events resulting in discontinuation from the study	4 (5)	2 (2)	12 (13)	8 (9)	26 (7)

The most commonly reported adverse events were diarrhea and nausea, followed by nasopharyngitis, flatulence, and vomiting (Table 4). For gastrointestinal disorders in general, as well as for diarrhea, a clear dose-response was observed but the incidences of nausea and vomiting were similar in the 10- and 15-mg JNJ-16269110 bid dose groups.

Table 4: Treatment-Emergent Adverse Events in at Least 5% of Subjects in Any Treatment Group by Preferred Term (Study R256918DIA2001: Safety Analysis Set)

		JNJ-16269110			
Dictionary-Derived Term	Placebo (N=88) n (%)	5 mg bid (N=84) n (%)	10 mg bid (N=90) n (%)	15 mg bid (N=89) n (%)	Total (N=351) n (%)
Total no. subjects with AEs	54 (61)	50 (60)	60 (67)	60 (67)	224 (64)
Diarrhoea	10 (11)	17 (20)	32 (36)	38 (43)	97 (28)
Nausea	4 (5)	4 (5)	13 (14)	13 (15)	34 (10)
Nasopharyngitis	9 (10)	8 (10)	6 (7)	6 (7)	29 (8)
Flatulence	2 (2)	2 (2)	8 (9)	10 (11)	22 (6)
Vomiting	2 (2)	4 (5)	9 (10)	7 (8)	22 (6)
Dizziness	6 (7)	3 (4)	4 (4)	3 (3)	16 (5)
Headache	3 (3)	3 (4)	5 (6)	4 (4)	15 (4)
Abdominal pain upper	0	3 (4)	3 (3)	8 (9)	14 (4)
Back pain	4 (5)	3 (4)	2 (2)	1 (1)	10 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.

Overall, JNJ-16269110 at doses of 5, 10, or 15 mg bid for 12 weeks demonstrated an acceptable safety profile in patients with T2DM and, aside from some gastrointestinal intolerance, was generally well tolerated. In general, gastrointestinal adverse events were mild or moderate in intensity, and were observed early following treatment, but tended to be less frequent with continued treatment. For the 10- and 15-mg JNJ-16269110 bid treatment groups, gastrointestinal-related adverse events were the most common reason

for discontinuation or interruption of treatment, with the majority occurring within the first 3 weeks of the study.

The majority of adverse events were mild or moderate in intensity. No subjects in the placebo treatment group had a severe adverse event. Severe adverse events that occurred during the study were diarrhea, nausea, vomiting, upper abdominal pain, cerebrovascular accident, pyrexia, and generalized rash. The majority of the severe gastrointestinal-related adverse events occurred in subjects treated with 15-mg JNJ-16269110 bid. The severe pyrexia and generalized rash were reported by 1 subject in the 10-mg JNJ-16269110 treatment group, and these events were considered serious.

The majority of gastrointestinal disorders reported as adverse events were assessed by the Investigator as possibly, probably, or very likely related to study drug. Other adverse events considered as very likely related to study drug were dizziness, chest pain, and hunger.

There were no deaths in this study; 5 subjects had a serious adverse event during the study. One of these subjects in the 10-mg JNJ-16269110 bid group reported generalized rash and pyrexia that were also considered SUAs (sudden, unexpected and associated adverse events). These events were considered by the Investigator as possibly related to study medication. The serious adverse event of generalized rash and pyrexia were associated with mucosal changes and skin exfoliation; increases in liver function tests were also observed. Overall there was no evidence of increased incidence of skin-related adverse events with JNJ-16269110 compared with placebo.

No treatment-related effects on mean values of transaminases were observed. Three subjects, all randomized to the 10-mg JNJ-16269110 bid group, experienced an increase in alanine aminotransferase (ALT) >3 time the upper limit of normal (ULN) during the treatment or follow-up phase.

There were no clear treatment-related effects on levels of fat soluble vitamins. No clinically relevant changes in other laboratory values, vital sign measurements, physical examination findings, or ECG abnormalities were noted in JNJ-16269110-treated subjects.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

Treatment with JNJ-16269110 at doses of 5, 10, or 15 mg bid for 12 weeks provided a small beneficial effect on HbA_{1c} levels in patients with T2DM treated with metformin monotherapy. Dose-dependent weight loss was observed for subjects treated with 10 and 15 mg JNJ-16269110 bid; weight loss in subjects treated with 5 mg JNJ-16269110 bid was comparable to placebo. The HbA_{1c} decrease observed with 10 and 15 mg JNJ-16269110 bid is in line with the observed weight loss, however, the data do not support a clinically meaningful, independent, antidiabetic effect of JNJ-16269110. Treatment with JNJ-16269110 at 10 or 15 mg bid was effective in decreasing fasting plasma glucose.

JNJ had a variable effect on lipids and lipoproteins (ie, cholesterol, LDL-C, HDL-C, VLDL, and LDL-C/HDL-C ratio) compared with placebo. Fasting triglyceride levels were increased in all 3 JNJ-16269110 treatment groups in a non-dose dependent fashion compared with placebo.

The plasma concentrations of JNJ-16269110 and its major metabolites, JNJ-16213119 and JNJ-2775188 (both inactive), were found to increase proportionally with increasing dose. Steady-state concentrations were reached by Week 4 for the parent compound JNJ-16269110 and the acid metabolite JNJ-16213119, and by Week 8 for the N-dealkyl metabolite JNJ-2775188.

Overall, JNJ-16269110 at doses of 5, 10, or 15 mg bid for 12 weeks demonstrated an acceptable safety profile in patients with T2DM and was generally well tolerated. Although gastrointestinal intolerance was observed early following treatment with JNJ-16269110, it tended to be less of an issue with continued treatment. There were no new clinically significant safety signals that would preclude further development of this compound.