SYNOPSIS

Issue Date: 27 January 2010
Document No.: EDMS-PSDB-10463684:2.0

Name of Sponsor/Company	Janssen-Cilag International N.V
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	paliperidone ER

Protocol No.: R076477SCH3020

Title of Study: A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With Schizophrenia

EudraCT Number: 2006-006967-22

Principal Investigator: Not applicable

Publication (Reference): None at the time of reporting

Study Period: From 29 August 2007 until 7 April 2009

Phase of Development: 3b

Objectives:

PRIMARY

The primary objective was to show that paliperidone extended release (ER) was superior to olanzapine in change of the triglyceride to high density lipoprotein ratio (TG:HDL ratio).

SECONDARY

Secondary objectives were to evaluate additional metabolic endpoints (see below) and to demonstrate non-inferiority of paliperidone ER versus olanzapine in efficacy as measured by Positive and Negative Syndrome Scale (PANSS).

Secondary metabolic parameters included:

- Changes in fasting insulin, total cholesterol, HDL, low density lipoproteins (LDL), TG, and glucose levels;
- Homeostatic model assessment of beta-cell function (HOMA2-%B) and homeostatic model assessment of insulin sensitivity (HOMA2-%S);
- 75 Oral gram Glucose Tolerance Test to assess insulin sensitivity and changes in insulin secretion as well as glycemic status (Impaired Fasting Glucose, Impaired Glucose Tolerance, Type 2 Diabetes);
- Changes in weight, body mass index (BMI) and waist;
- New onset or presence of metabolic syndrome during treatment according to National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) criteria.

Other secondary endpoints were:

- PANSS subscale scores;
- Clinical Global Impression-Severity score (CGI-S);
- Short Form Health Survey 36® (SF-36) subscales: 'Role Emotional', 'Mental Health', 'Social Functioning' and 'Vitality' ;

- Quality of sleep and daytime drowsiness (categorical scale).

Overall safety was assessed.

Methods:

This trial was a prospective randomized open-label parallel-group multicenter 6-month study which was aimed to compare the metabolic effects of paliperidone ER and olanzapine in subjects with schizophrenia. Subjects previously treated with any oral antipsychotic except paliperidone ER, olanzapine or clozapine could be enrolled and were treated with flexibly dosed paliperidone ER (6 to 9 mg) or olanzapine (10 to 15 mg) once daily. Subjects were stratified according to the metabolic effects of their previous antipsychotic medication (weight neutral versus not neutral). Approximately 456 subjects (228 subjects in each randomization group) were planned to participate.

A planned interim analysis was performed after the first 152 subjects had completed the first 3 months of the study. If there was a substantial number of protocol violators (e.g., >10%), an additional per-protocol analysis could be performed. As 117 (25.5%) subjects had a major protocol deviation, a per-protocol analysis was performed.

Number of Subjects (planned and analyzed):

The planned total sample size was approximately 456 adult subjects (228 in each treatment group). For the number of subjects randomized, randomized and treated, and included in the several analysis sets, please see the table below.

Subject Disposition

	Paliperidone ER N	Olanzapine N	Total N
Screened	-	-	510
Randomized	-	-	462
Randomized and treated	239	220	459
Interim analysis	80	72	152
Primary endpoint analysis	215	198	413
Secondary endpoint analysis	239	220	459
Safety analysis	239	220	459
Per-protocol analysis	178	164	342

N=number of subjects with data
All treated subjects are those who received at least one dose of trial medication.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria: Subjects enrolled in this study were required to meet the following acceptance criteria:

- Male or female, between 18 and 65 years of age, inclusive;
- Subject met the DSM-IV criteria for schizophrenia;
- Subject had a PANSS total score at screening of 60 to 100, inclusive;
- Subject had to, in the opinion of the investigator, benefit from treatment with paliperidone ER or olanzapine;
- Subjects on lipid-lowering therapy had to be on a stable dose for at least 4 weeks for statins, niacin, ezetimibe and resins or for at least 12 weeks for fibrates.
- Subject was able to read, understand and sign the IRB-approved informed consent form;
- Female subjects had to be postmenopausal (for at least 1 year), surgically sterile, abstinent, or, if sexually active, be practicing and effective method of birth control (e.g. prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; women of child-bearing potential had to have a negative urine pregnancy test at screening;
- Subject was healthy on the basis of a physical examination and vital signs at screening;
- Subject had to be able and willing to fill out self-administered questionnaires.

Exclusion Criteria: Subjects were not to be enrolled into the study if it was determined upon prestudy examination that:

- Subject had previously been treated with paliperidone ER, olanzapine, or clozapine within the past 6 months or had never been treated with an antipsychotic before;
- Treatment with a depot antipsychotic within the past 3 months;
- Treatment with a mood stabilizer or a recently initiated antidepressant ($\leq$ 3 months);
- Subject had a history of diabetes or currently receiving a glucose-lowering agent to treat diabetes;
- Subject had abnormal fasting plasma glucose (>126 mg/dL) or fasting TG levels (>400 mg/dL) at screening;
- Subject had, at the discretion of the investigator, clinically relevant abnormal laboratory values at screening;
- Relevant history of any significant and/or unstable cardiovascular, respiratory, neurologic (including seizures or significant cerebrovascular), renal, hepatic, endocrine, or immunologic diseases, including recent or present clinically relevant laboratory abnormalities (as deemed by the investigator);
- History or current symptoms of tardive dyskinesia;
- History of neuroleptic malignant syndrome;
- Pregnant or breast-feeding female;

- Known hypersensitivity to paliperidone ER, risperidone or olanzapine;
- Judged to be at high risk for or presence of violence or self-harm;
- Inability to swallow the study medication whole with the aid of water (subjects may not chew, divide, dissolve, or crush the study medication, as this may affect the release profile);
- Subjects with a narrowing or blockage of their gastro-intestinal tract;
- Employees of the investigator or study center, persons with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or family members of the employees or the investigator;
- Subjects with current or known history (over the past 6 months) of substance dependence according to DSM-IV Criteria;
- Had received an experimental drug or used an experimental medical device within 30 days before the planned start of treatment.

Test Product, Dose and Mode of Administration, Batch No.:

The paliperidone ER (INVEGA®) starting dose was 6 mg/day in most subjects. Some subjects who could benefit from a higher dose could have been started on 9 or 12 mg/day. Doses could be changed within the mentioned dose range throughout the study.

Study Medication	Batch Number	Expiry Date
Paliperidone ER 3-mg and 6-mg tablet kits	0620766 (3-mg tablets)	August 2008
	0716337 (3-mg tablets)	October 2008*
	0729774 (3-mg tablets)	October 2010
	0607491 (6-mg tablets)	June 2008
	0707704 (6-mg tablets)	November 2009
	0729777 (6-mg tablets)	October 2010

* expiry date extended with 12 months

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

Reference therapy was olanzapine (Zyprexa®). The olanzapine starting dose was 10 mg/day in most subjects. Some subjects who could benefit from a higher dose could have been started on 15 mg/day. Doses could be changed within the mentioned dose range throughout the study.

Study Medication	Batch Number	Expiry Date
Olanzapine 5-mg and 10-mg tablet kits	A209677/2 (5-mg tablets)	March 2009
	A476904 (5-mg tablets)	December 2010
	A205097 (10-mg tablets)	March 2009
	A446574 (10-mg tablets)	September 2010
	A494029 (10-mg tablets)	November 2010

Duration of Treatment: 6 months

Criteria for Evaluation:

All subjects who received at least one dose of paliperidone ER or olanzapine and had at least one post-baseline assessment were included in the analyses, i.e., the intent-to-treat (ITT) population.

Metabolic measures (baseline to endpoint) included the following:

Primary:

- Change from baseline to endpoint in the TG:HDL ratio.

Secondary:

- Change in fasting insulin, total cholesterol, HDL, LDL, TG, and glucose levels;
- Homeostatic model assessment of beta-cell function (HOMA2-%B) and homeostatic model assessment of insulin sensitivity (HOMA2-%S);
- The need to change the dose of existing lipid-lowering medications;
- Number of new uses of or increase in antihypertensive medications;
- Onset of type 2 diabetes mellitus (i.e., fasting plasma glucose [FPG] ≥126 mg/dL or 2-hour post-load plasma glucose ≥200 mg/dL during an oral glucose tolerance test [OGTT] or initiated use of glucose-lowering agents during the course of the study);
- Onset of Impaired Glucose Tolerance or IGT (i.e., 2-hour post-load plasma glucose ≥140 mg/dL but <200 mg/dL in an OGTT);
- Impaired Fasting Glucose or IFG (FPG ≥100 mg/dL and <126 mg/dL);
- Changes in body weight, BMI and waist;
- New onset or presence of metabolic syndrome during treatment according to NCEP/ATP III criteria;

Other secondary measures (changes from baseline to endpoint) included the following:

- Total PANSS and PANSS subscale scores;
- CGI-S;
- SF-36 subscales 'Role Emotional', 'Mental Health', 'Social Functioning', and 'Vitality';
- Quality of sleep and daytime drowsiness (categorical scale).

Safety measures included the following:

- Adverse events (AEs): Subjects were instructed to report AEs as they emerged and were assessed at each study visit after informed consent had been obtained until the last study-related procedure.
- Laboratory tests: were performed at screening, at baseline, after 3 months treatment and at the end of the study (6 months) or at the time of discontinuation (endpoint). An OGTT for glucose and insulin was performed at baseline, after 3 months treatment and at the end of the study (6 months) or at the time of discontinuation (endpoint). A urine pregnancy test was completed at screening and at the end of the study or at the time of discontinuation (endpoint) in all females of childbearing potential.
- Vital signs and weight: were assessed at screening, at baseline, after 6 weeks treatment, after 3 months treatment and at the end of the study or at the time of discontinuation (endpoint).
- Physical examination: was completed at screening and at the end of the study (6 months treatment) or at the time of discontinuation (endpoint).

Statistical Methods: Descriptive statistics, intent-to-treat analysis, frequency tabulations, Wilcoxon two-sample test (2-tailed), Wilcoxon signed rank test (2-tailed), Fisher's exact test (2-tailed), Schuirmann's test

RESULTS:

Overall, 346 out of 459 subjects (75.4%) completed the trial. Seventy-one (29.7%) subjects in the paliperidone ER and 42 (19.1%) subjects in the olanzapine group discontinued the study. The major reason for discontinuation was withdrawal of consent (52 [11.3%] subjects) followed by lack of efficacy (21 [4.6%]). Sixteen (3.5%) subjects discontinued due to an AE.

Two subjects were discontinued from the study due to glucose-related AEs, i.e., 1 subject in the paliperidone ER group due to hyperglycemia and 1 subject in the olanzapine group due to blood glucose increased. One subject (olanzapine group) was discontinued from the study due to weight increased. Seven (2.9%) subjects of the paliperidone ER group and 1 (0.5%) subject of the olanzapine group discontinued the study due to non-compliance.

Completion/Withdrawal Information
(R076477SCH3020 Study: All Subjects)

n (%)	Paliperidone ER N=239	Olanzapine N=220	Total N=459
Completed	168 (70.3)	178 (80.9)	346 (75.4)
Withdrawn	71 (29.7)	42 (19.1)	113 (24.6)
Withdrawal of consent	30 (12.6)	22 (10.0)	52 (11.3)
Lack of efficacy	15 (6.3)	6 (2.7)	21 (4.6)
AE	11 (4.6)	5 (2.3)	16 (3.5)
Lost to follow-up	6 (2.5)	4 (1.8)	10 (2.2)
Other[a]	9 (3.8)	5 (2.3)	14 (3.1)

N=number of subjects with data, n=number of subjects with that observation
[a] Non-compliance, incorrect olanzapine dose, screening PANSS score too high (Sponsor's decision), subject was not admitted, and investigator mistake

The majority of the subjects were male (266 [58.0%] subjects). Mean (SD) age was 38.2 (11.2) years. At baseline, the mean (SD) TG:HDL ratio was 1.48 (1.276) for subjects in the paliperidone ER group and 1.29 (0.901) for subjects in the olanzapine group. Demographic and baseline characteristics of the olanzapine and paliperidone ER groups were not statistically significantly different ($p>0.05$), except for pulse rate which was statistically significantly higher in the olanzapine group ($p=0.0406$).

Demographic and Baseline Characteristics
(R076477SCH3020 Study: ITT Analysis Set)

Parameter	Paliperidone ER	Olanzapine	Total
Gender, n (%)			
N	239	220	459
Female	106 (44.4)	87 (39.5)	193 (42.0)
Male	133 (55.6)	133 (60.5)	266 (58.0)
Age (years)			
N	239	220	459
Mean (SD)	38.8 (11.1)	37.5 (11.4)	38.2 (11.2)
Median	36.7	36.2	36.4
Range	18 - 65	19 - 65	18 - 65
TG:HDL ratio			
N	235	219	-
Mean (SD)	1.48 (1.276)	1.29 (0.901)	-
Median	1.15	1.02	-
Range	0.26 - 10.48	0.24 - 6.05	-
Weight (kg)			
N	239	220	459
Mean (SD)	76.0 (17.0)	77.9 (16.4)	76.9 (16.7)
Median	74.0	78.0	75.7
Range	40 - 135	41 - 133	40 - 135
BMI (kg/m^2)			
N	239	220	459
Mean (SD)	26.9 (6.32)	27.0 (5.71)	27.0 (6.0)
Median	25.5	26.4	26.1
Range	16.6 - 53.2	16.6 - 51.0	16.6 - 53.2
Waist (cm)			
N	235	219	454
Mean (SD)	92.5 (14.6)	93.4 (15.5)	92.9 (15.0)
Median	91.0	93.0	92.0
Range	58 - 147	58 - 140	58 - 147
Pulse rate (bpm)			
N	237	220	457
Mean (SD)	77.0 (10.0)	79.7 (11.6)	78.3 (10.9)
Median	77.0	80.0	78.0
Range	40 - 102	55 - 120	40 - 120
Systolic blood pressure (mmHg)			
N	239	220	459
Mean (SD)	120.4 (13.1)	119.9 (13.4)	120.2 (13.3)
Median	120.0	120.0	120.0
Range	90 - 165	90 - 161	90 - 165
Diastolic blood pressure (mmHg)			
N	239	220	459
Mean (SD)	76.8 (9.4)	76.3 (9.9)	76.6 (9.6)
Median	77.0	76.0	76.0
Range	50 - 112	50 - 103	50 - 112

N=number of subjects with data; n=number of subjects with that observation

Primary Endpoint Analysis

The primary endpoint analysis set consisted of 413 subjects, i.e., all subjects who received study medication at least once and had baseline and post-baseline TG and HDL data. Data of subjects with missing TG or HDL values or who started or changed lipid lowering medication during the study were excluded from analysis.

The results of the primary endpoint, the change from baseline to endpoint in the TG:HDL ratio, is presented in the table below. At endpoint, the TG:HDL ratio in the paliperidone ER group was not statistically significantly changed versus baseline with a mean (SD) value of -0.08 (1.10). In the olanzapine group, the TG:HDL ratio was statistically significantly increased (i.e., worsened) versus baseline at endpoint with a value of 0.42 (1.19) ($p<0.0001$), mainly due to an increase in TG over time. Since the difference between the treatment groups in change versus baseline at endpoint in TG:HDL ratio was statistically significant ($p<0.0001$), the null hypothesis of no difference in change versus baseline at endpoint in TG:HDL ratio could be rejected.

Primary Endpoint: Actual Values and Changes From Baseline in TG:HDL Ratio During the Study (R076477SCH3020 Study: Primary Endpoint Analysis Set)

	Actual TG:HDL ratio		Change from baseline in TG:HDL ratio	
Timepoint	Paliperidone ER	Olanzapine	Paliperidone ER	Olanzapine
Baseline				
N	215	198	-	-
Mean (SD)	1.49 (1.30)	1.24 (0.82)	-	-
Median	1.15	1.01	-	-
Range	0.26 - 10.48	0.24 - 6.05	-	-
p-value [a]	-	0.2038	-	-
p-value [b]	-	-	-	-
Month 3				
N	187	180	187	180
Mean (SD)	1.39 (1.11)	1.67 (1.83)	-0.11 (1.16)	0.42 (1.46)
Median	1.04	1.13	-0.02	0.12
Range	0.25 - 6.80	0.30 - 15.83	-8.94 - 3.58	-1.94 - 12.87
p-value [a]	-	0.0702	-	0.0002
p-value [b]	-	-	0.2744	< 0.0001
Month 6				
N	158	171	158	171
Mean (SD)	1.45 (1.12)	1.72 (1.54)	-0.06 (1.19)	0.45 (1.23)
Median	1.06	1.26	-0.02	0.27
Range	0.27 - 6.49	0.24 - 13.28	-8.49 - 3.41	-2.71 - 10.32
p-value [a]	-	0.0445	-	< 0.0001
p-value [b]	-	-	0.6726	< 0.0001
Endpoint				
N	215	198	215	198
Mean (SD)	1.41 (1.06)	1.66 (1.46)	-0.08 (1.10)	0.42 (1.19)
Median	1.04	1.19	-0.02	0.22
Range	0.22 - 6.49	0.24 - 13.28	-8.49 - 3.41	-2.71 - 10.32
p-value [a]	-	0.0330	-	< 0.0001
p-value [b]	-	-	0.4718	< 0.0001

N=number of subjects with data

[a] Between-group difference using a Wilcoxon two-sample test, 2-tailed

[b] Within-group difference using a Wilcoxon signed rank test, 2-tailed

Secondary Endpoint Analysis

The secondary endpoint analysis set included all subjects who received study medication at least once and provided ≥1 post-baseline efficacy measurement.

Non-inferiority Testing of Efficacy

Non-inferiority testing by means of the Schuirmann's test showed that the difference in change versus baseline at endpoint (3.1070) was statistically significantly lower ($p<0.0001$) than the minimum of the clinically relevant difference in the ITT population. Therefore, the null hypothesis of non-equivalence was rejected and equivalence to within the specified equivalence bounds could be claimed.

However, in the Per-Protocol population testing non-inferiority of the paliperidone ER treatment group compared to the olanzapine treatment group showed that the difference in change from baseline in total PANSS (4.5725) between both treatment groups was not statistically significantly lower than the minimum of the clinically relevant difference ($p=0.1870$). The Schuirmann's test did not reject the null hypotheses of non-equivalence so that equivalence within the specified equivalence bound could not be claimed.

Metabolic Endpoints

For subjects with **impaired LDL** defined as ≥100 mg/dL or ≥130 mg/dL, no statistically significant difference was observed between paliperidone ER and olanzapine treatment at all timepoints and endpoint. Of the subjects who did not have a LDL level ≥100 mg/dL at baseline and who had ≥1 valid postbaseline assessment, a large part in both treatment groups had a first onset of LDL ≥100 mg/dL during the 6-month treatment period: 63 (70.0%) subjects in the paliperidone ER group and 50 (61.7%) subjects in the olanzapine group (no statistically significant difference). Of the subjects who did not have a LDL level ≥130 mg/dL at baseline and who had ≥1 valid postbaseline assessment, 35 (26.1%) and 40 (28.8%) subjects in the paliperidone ER and olanzapine group, respectively, had a first onset of LDL mg/dL during the 6-month treatment period (no statistically significant difference). For the majority of subjects with impaired LDL defined as ≥100 mg/dL or ≥130 mg/dL, the first onset of that level was observed at Month 3.

For subjects with **impaired TG** (defined as a TG level ≥150 mg/dL), no statistically significant difference was observed between paliperidone ER and olanzapine treatment at any timepoint or endpoint. However, of the subjects who did not have impaired TG at baseline and who had ≥1 valid postbaseline assessment, a statistically significantly lower number of subjects in the paliperidone ER group had a first onset of impaired TG during the 6-month treatment period (31 [27.0%] subjects) compared to subjects in the olanzapine group (53 [39.8%] subjects) ($p=0.0433$). The first onset of impaired TG was for the majority of subjects in the olanzapine group at Month 3 (36 [67.9%] subjects), while for subjects in the paliperidone ER group the number was comparable at Month 3 (15 [48.4%] subjects) and Month 6 (13 [41.9%] subjects).

The number of subjects with **impaired HDL** (defined as a HDL level <40 mg/dL) remained constant over time for both treatment groups and no statistically significant between-group difference was observed at any timepoint or endpoint. Of the subjects who did not have impaired HDL at baseline and who had ≥1 valid postbaseline assessment, 22 (19.8%) subjects in the paliperidone ER group and 31 (23.8%) subjects in the olanzapine group had a first onset of impaired HDL during the 6 month treatment (no statistically significant difference). In both treatment groups the first onset of impaired HDL occurred at Month 3 for the majority of subjects.

Onset of **IGT** was defined as a 2-hour post-load plasma glucose of firstly as ≥140 mg/dL but <200 mg/dL after a 75 gram OGTT and secondly as ≥200 mg/dL. The difference between paliperidone ER and olanzapine treatment was not statistically significant at any assessed timepoint or endpoint. Of the subjects who did not have impaired IGT at baseline and who had ≥1 valid postbaseline assessment, 29 (19.1%) subjects in the paliperidone ER group and 37 (23.9%) subjects in the olanzapine group had a first onset of IGT (glucose ≥140 but <200 mg/dL) during treatment (no statistically significant difference). In the paliperidone ER group, the first onset of IGT (glucose ≥140 but <200 mg/dL) occurred at Month 3 for the majority of subjects (20 [69.0%] subjects) while for olanzapine a comparable number of subjects was observed with first onset at Month 3 (19 [51.4%] subjects) or Month 6 (17 [45.9%] subjects). Impaired glucose tolerance (glucose ≥200 mg/dL) was observed for at most 5% of subjects in either treatment group at any timepoint (no statistically significant within-group or between-group differences).

Onset of **IFG** was defined as a post-baseline glucose under fasted conditions ≥100 mg/dL but <126 mg/dL. The difference between paliperidone ER and olanzapine treatment was not statistically significant at any assessed timepoint or endpoint.

Beta-cell Function, Insulin Sensitivity, and Insulin Secretion

The **HOMA-IR** data of the olanzapine group showed a statistically significant increase in mean (SD) IR from 2.24 (4.13) at baseline to 2.67 (4.07) at endpoint (change: 0.43 [5.37], p=0.0003), whereas in the paliperidone ER group HOMA-IR remained virtually unchanged during treatment (baseline value: 2.26 [2.64]; change at endpoint: 0.28 [5.39], p=0.1507). Comparison of the changes versus baseline between the two treatment groups showed a strong trend towards a statistically significant lower HOMA-IR after 6 months of paliperidone ER treatment (mean [SD] change: -0.23 [3.06]) compared to olanzapine treatment (mean [SD] change: 0.45 [5.83], p=0.0561).

Beta-cell function assessed using HOMA (**HOMA-%B**) in the olanzapine group showed a trend towards a statistically significant increased insulin secretion compared to baseline at all timepoints and endpoint. In the paliperidone group, insulin secretion was virtually unchanged during treatment (no statistically significant change). Although the differences between treatment groups in absolute values of insulin secretion did not reach statistical significance, the changes versus baseline proved to be statistically significantly higher in the olanzapine group than in the paliperidone ER group at all timepoints and endpoint.

The **insulinogenic index**, used as a measure of early insulin secretion in response to the OGTT, was statistically significantly increased in the olanzapine group with 39.06 (279.65) pM/mM versus baseline (128.66 [150.00] pM/mM) at Month 6 (p=0.0478). A trend towards significance was observed for the change from baseline at endpoint (p=0.0629). During paliperidone ER treatment, the mean (SD) insulinogenic index remained constant after baseline (value: 135.98 [150.65] pM/mM). The difference between paliperidone ER and olanzapine treatment was not statistically significant at any assessed timepoint or endpoint.

Insulin secretion was also assessed using the entire OGTT time profile using a simplified version of the method described by Mari et al. This analysis accounted for any differences in plasma glucose concentrations by determining the relationship between plasma insulin and plasma glucose concentrations using regression analysis. Glucose sensitivity for insulin secretion (defined as the slope of the relationship between plasma insulin and plasma glucose) in the olanzapine group was statistically significantly increased at all timepoints and endpoint compared to baseline. No statistically significant changes from baseline were observed during paliperidone ER treatment. All between-group differences were not statistically significant.

The insulin concentrations at 5, 7, and 9 mM plasma glucose concentrations were consistently, but not statistically significantly, lower during the 6-month paliperidone ER treatment than during olanzapine treatment. For all 3 glucose concentrations, the insulin concentration statistically significantly increased compared to baseline at Month 6 and endpoint in the olanzapine group and showed trends toward statistically significant increase at endpoint in the paliperidone ER group. Although the change versus baseline was consistently higher in the olanzapine group throughout the treatment, the between-group differences were not statistically significant, probably because of large standard deviations in both groups.

In summary, these results suggest that treatment with olanzapine led to decreased insulin sensitivity with compensatory increases in insulin release, whereas treatment with paliperidone ER led to small changes in these parameters.

Onset of T2DM and Metabolic Syndrome

No statistically significant difference was observed in the number of subjects with onset of T2DM after 6 months treatment with paliperidone ER or olanzapine. However, the number of subjects with a new onset of metabolic syndrome during the 6-month treatment period was statistically significantly lower in the paliperidone ER group (23 [13.2%] subjects) compared to the olanzapine group (38 [23.3%] subjects) ($p=0.0230$).

Other Secondary Endpoints

Positive and Negative Syndrome Scale

In both treatment groups, the total PANSS score showed a gradual improvement of symptoms over the 6-month treatment period with a statistically significant change from baseline at all post-baseline assessments. The three subscale scores, i.e., the positive, negative, and general psychopathology PANSS subscales, all showed a gradual improvement of symptoms during treatment with a statistically significant change from baseline at all post-baseline assessments ($p<0.0001$).

The PANSS response rate was calculated using a correction for the minimum PANSS value of 30. The number of subjects with at least 20%, 30%, 40%, and 50% improvement in total PANSS score compared to baseline gradually increased over the 6-month treatment period in both treatment groups. In the paliperidone ER group, 141 (60.3%) subjects had an improvement in total PANSS of at least 20% at endpoint compared to baseline and 75 (32.1%) subjects had a response rate of at least 50%. Values in the olanzapine group were 141 (65.9%) and 68 (31.8%) subjects, respectively. None of the between-group differences were statistically significant for any response rate at any timepoint.

Clinical Global Impression - Severity

At baseline, the mean (SD) CGI-S score was similar in the paliperidone ER group (3.26 [0.82]) and the olanzapine group (3.29 [0.74]) (no statistically significant difference). After baseline, a consistent decrease (i.e., improvement in the severity of the disease) in mean CGI-S score over time was observed in both treatment groups, with statistically significant changes from baseline at all timepoints and endpoint. A trend towards a statistically significant larger decrease versus baseline was observed for olanzapine treatment compared to paliperidone ER treatment at endpoint ($p=0.0587$), however, the between-group difference (0.15 points) was not considered clinically relevant.

Short Form Health Survey 36®

In the olanzapine group, the PCS was statistically significantly better at endpoint compared to baseline ($p<0.0001$), while in the paliperidone ER group, scores remained virtually unchanged over the 6-month treatment period (no statistically significant change). No statistically significant difference was observed between paliperidone ER and olanzapine treatment.

For the MCS, the mean (SD) baseline score was statistically significantly higher in the paliperidone ER group (37.07 [11.81]) than in the olanzapine group (33.93 [13.22]) (p=0.0095), but the difference was not considered clinically relevant. At endpoint, mental health was statistically significantly improved compared to baseline in both treatment groups (p<0.0001), with a statistically significantly larger improvement in the olanzapine group compared to the paliperidone ER group (p=0.0284).

Quality of Sleep

The quality of sleep over the past 7 days was statistically significantly improved at endpoint compared to baseline in both treatment groups. No statistically significant difference was observed in changes from baseline at endpoint.

SAFETY RESULTS:

A summary of the treatment-emergent AEs (TEAEs) during treatment is presented in the table below.

Summary of Treatment-Emergent Adverse Events During the Study
(R076477SCH3020 Study: Safety Analysis Set)

Number of subjects (n [%]) with	Paliperidone ER N=239	Olanzapine N=220	Total N=459
At least one TEAE	130 (54.4)	114 (51.8)	244 (53.2)
At least one treatment-emergent SAE	21 (8.8)	12 (5.5)	33 (7.2)
At least one TEAE that was considered possibly, probably, or very likely related to study medication by the investigator	77 (32.2)	84 (38.2)	161 (35.1)
At least one severe TEAE	14 (5.9)	12 (5.5)	26 (5.7)
At least one TEAE leading to discontinuation of the study	11 (4.6)	5 (2.3)	16 (3.5)

N=number of subjects with data; n=number of subjects with one or more event

Overall 244 (53.2%) subjects had at least one TEAE, with 130 (54.4%) subjects in the paliperidone ER group and 114 (51.8%) subjects in the olanzapine group.

No deaths were reported. A total of 33 (7.2%) subjects had at least one treatment-emergent SAE of which 21 (8.8%) subjects in the paliperidone ER group and 12 (5.5%) subjects in the olanzapine group. Sixteen (3.5%) subjects discontinued the study due to a TEAE.

An overview of the TEAEs reported by >1% of all subjects during the study is provided in the table below.

Treatment-Emergent Adverse Events Reported by >1% of all Subjects During the Study by Decreasing Total Number of Subjects
(R076477SCH3020 Study: Safety Analysis Set)

System organ class, Preferred term, n (%)	Paliperidone ER N=239	Olanzapine N=220	Total N=459
Subjects with at least one TEAE	130 (54.4)	114 (51.8)	244 (53.2)
Investigations	35 (14.6)	55 (25.0)	90 (19.6)
Weight increased	23 (9.6)	40 (18.2)	63 (13.7)
Blood creatine phosphokinase increased	7 (2.9)	5 (2.3)	12 (2.6)
Psychiatric disorders	61 (25.5)	24 (10.9)	85 (18.5)
Insomnia	23 (9.6)	3 (1.4)	26 (5.7)
Schizophrenia	12 (5.0)	4 (1.8)	16 (3.5)
Anxiety	10 (4.2)	3 (1.4)	13 (2.8)
Psychotic disorder	9 (3.8)	2 (0.9)	11 (2.4)
Tension	5 (2.1)	1 (0.5)	6 (1.3)
Agitation	4 (1.7)	1 (0.5)	5 (1.1)
Depression	2 (0.8)	3 (1.4)	5 (1.1)
Nervous system disorders	40 (16.7)	40 (18.2)	80 (17.4)
Somnolence	8 (3.3)	21 (9.5)	29 (6.3)
Headache	11 (4.6)	9 (4.1)	20 (4.4)
Sedation	5 (2.1)	6 (2.7)	11 (2.4)
Akathisia	6 (2.5)	2 (0.9)	8 (1.7)
Dizziness	5 (2.1)	2 (0.9)	7 (1.5)
Dyskinesia	3 (1.3)	2 (0.9)	5 (1.1)
Hypersomnia	3 (1.3)	2 (0.9)	5 (1.1)
Infections and infestations	15 (6.3)	14 (6.4)	29 (6.3)
Influenza	2 (0.8)	3 (1.4)	5 (1.1)
Gastrointestinal disorders	17 (7.1)	10 (4.5)	27 (5.9)
Dyspepsia	4 (1.7)	2 (0.9)	6 (1.3)
Metabolism and nutrition disorders	8 (3.3)	13 (5.9)	21 (4.6)
Increased appetite	4 (1.7)	5 (2.3)	9 (2.0)
General disorders and administration site conditions	11 (4.6)	8 (3.6)	19 (4.1)
Fatigue	6 (2.5)	2 (0.9)	8 (1.7)
Irritability	3 (1.3)	3 (1.4)	6 (1.3)
Reproductive system and breast disorders	11 (4.6)	0	11 (2.4)
Amenorrhea	8 (3.3)	0	8 (1.7)
Vascular disorders	3 (1.3)	5 (2.3)	8 (1.7)
Hypertension	2 (0.8)	3 (1.4)	5 (1.1)

N=number of subjects with data; n=number of subjects with one or more event

The most frequently reported TEAEs were weight increased (23 [9.6%] subjects in the paliperidone ER group and 40 [18.2%] subjects in the olanzapine group), somnolence (8 [3.3%] and 21 [9.5%] subjects, respectively), insomnia (23 [9.6%] and 3 [1.4%] subjects, respectively), and schizophrenia (12 [5.0%] and 4 [1.8] subjects, respectively).

Of the most frequently observed treatment-emergent laboratory abnormalities creatine kinase and ALT higher than normal were observed with a higher number of subjects in the olanzapine group compared to the paliperidone ER group. Cholesterol higher and lower than normal and LDL lower than normal were observed with comparable number of subjects in both treatment groups. The number of subjects with laboratory abnormalities reported as TEAE was low per preferred term.

At baseline subjects in the olanzapine treatment group weighed slightly more than those in the paliperidone ER group (mean [SD] values: 77.85 [16.28] kg and 75.75 [16.71] kg, respectively), but the difference was not statistically significant. Body weight gradually increased compared to baseline at all timepoints and endpoint in both treatment groups. However, subjects receiving olanzapine treatment weighed statistically significantly more compared to those receiving paliperidone ER at each timepoint and their weight gain was also statistically significantly larger.

BMI results were similar to those of body weight. The mean (SD) BMI at baseline was comparable between the paliperidone ER (26.84 [6.28] kg/m²) and olanzapine (26.95 [5.72] kg/m²) group. BMI gradually increased over time in both treatment groups but the increase versus baseline was statistically significantly larger in the olanzapine group compared to the paliperidone ER group at all timepoints and endpoint.

At baseline, the mean (SD) pulse rate in the paliperidone ER group (76.98 [9.96] mmHg) was statistically significantly lower than in the olanzapine group (79.77 [11.61] mmHg). At endpoint, actual values of pulse rate were not statistically significantly different between the paliperidone ER and olanzapine group, but the changes from baseline were (p=0.0351). Changes in blood pressure were small and no between-group difference was observed.

STUDY LIMITATIONS: Open-label design

CONCLUSION:

The changes in TG:HDL ratio versus baseline were statistically significantly in favor of paliperidone ER treatment compared to olanzapine treatment. Data suggest that olanzapine led to decreased insulin sensitivity with compensatory increases in insulin release, whereas treatment with paliperidone ER led to small changes in these parameters. Results showed that paliperidone ER is as efficacious as olanzapine in symptom reduction of schizophrenia. The severity of the disease and physical and mental health of subjects improved after a 6 month treatment with paliperidone ER or olanzapine.

Paliperidone ER led to statistically significantly less weight gain than olanzapine and fewer subjects were reported with the AE of weight gain in the paliperidone ER group than in the olanzapine group. After 6 months of treatment, a statistically significantly higher number of subjects in the olanzapine group met the criteria of new-onset metabolic syndrome compared to subjects in the paliperidone ER group. This observation is consistent with previous clinical studies that indicated that some atypical antipsychotic medications like olanzapine have a side effect profile including significant weight gain and metabolic changes.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.