SYNOPSIS

Issue Date: 15 October 2010
Document No.: EDMS-ERI-15961405: 1.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-37822681

Protocol No.: 37822681SCH2002

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of 3 Fixed Doses of JNJ-37822681 Administered Twice-Daily in Subjects with Schizophrenia

EudraCT Number: 2007-007083-22

Principal Investigator: Kaire Aadamsoo, MD, North Estonian Regional Hospital Clinic of Psychiatry, Estonia

Publication (Reference): None

Study Period: 19 November 2008 to 01 February 2010; database lock date: 26 February 2010

Phase of Development: Phase 2

Objectives: The primary objective was to evaluate the efficacy of JNJ-37822681 via changes from baseline in the total Positive and Negative Syndrome Scale (PANSS) score of 3 fixed doses (10, 20, and 30 mg twice daily) of JNJ-37822681 compared with placebo after 6 weeks of treatment in subjects with schizophrenia.

The secondary objectives were:

- To evaluate the safety of 3 fixed doses (10, 20, and 30 mg) of JNJ-37822681 in subjects with schizophrenia;
- To assess the effect of JNJ-37822681 on the changes from baseline in the PANSS subscales and the Clinical Global Impression of Severity (CGI-S) of illness compared with placebo at 6 weeks, and compared with olanzapine at 12 weeks;
- To assess the effect of JNJ-37822681 on the changes from baseline in body mass index (BMI), body weight, plasma metabolic endpoints (fasting total cholesterol, triglycerides, high-density lipoproteins [HDL], low-density lipoproteins [LDL], very-low-density lipoproteins [VLDL], free fatty acids, glycosylated hemoglobin [HbA1c], glucose, and insulin) and Subjective Well-being under Neuroleptics (SWN) compared with olanzapine and placebo during the first 6-week period, and compared with olanzapine during the 12-week period;

- To assess the acute response to JNJ-37822681 relative to placebo and olanzapine using the changes from baseline in the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) in the first 2 weeks while subjects were hospitalized;
- To explore the pharmacokinetics (PK) and the relationship between pharmacokinetics and efficacy parameters (eg, change in PANSS scores) and safety parameters (eg, treatment emergent extrapyramidal symptoms [EPS], or other adverse events);
- To explore genes/genotypes that could be related to clinical response or non-response, to safety parameters, or to pharmacokinetics of JNJ 37822681.

Methods: This was a multicenter, double-blind, randomized, placebo- and active controlled, parallel-group, dose-response study in men and women with schizophrenia. Following a screening period (Day –21 to –5), subjects were randomly assigned to 1 of the 5 treatment groups to receive oral doses of JNJ-37822681 (10, 20 or 30 mg twice-daily) for 12 weeks, olanzapine 15-mg once-daily for 12 weeks, or placebo for 6 weeks followed by olanzapine 15 mg once-daily for the remaining 6 weeks. Olanzapine was initiated at dose of 10 mg once-daily for 1 week and then increased to 15 mg once-daily for the remainder of the treatment period for both groups receiving olanzapine.

All subjects were hospitalized during the first 2 weeks of treatment for detailed follow-up of safety and disease status. As early as Day 15, subjects were discharged from the hospital and followed as outpatients if they were believed by the investigator to be at no significant risk of suicidal or violent behavior and if their CGI-S was 4 (moderately ill) or less. Thereafter subjects visited the study center weekly during the next 6 weeks of the treatment and every 2 weeks until Week 13 for evaluation of disease status and safety. The total study duration did not exceed 16 weeks for each subject.

Efficacy of the primary endpoint (change in PANSS total score) was assessed at 6 weeks. Secondary endpoints including PANSS subscales, CGI-S, plasma markers for lipid and glucose metabolism, BMI, and body weight as well as evaluation of subjective well-being were assessed after 6 and 12 weeks of treatment (except NOSIE, which was only evaluated the first 2 weeks while subjects were hospitalized).

A poststudy visit for collection of additional safety data was scheduled for 1 week after a subject's final dose of study drug. An interim analysis was to be conducted, dependent on recruitment rate, when 50% of the planned subjects had completed 6 weeks of treatment.

Number of Subjects (planned and analyzed): 475 subjects were planned to be randomized in this study (95 subjects per treatment group).

A total of 498 subjects with schizophrenia were randomly assigned to treatment. Of these, 496 subjects received at least 1 dose of study drug and were included in the safety analysis set, with 100 subjects in the placebo/olanzapine group, 99, 104, and 100 subjects in the 10-, 20, and 30-mg JNJ-37822681 twice-daily groups, respectively, and 93 subjects in the 15-mg olanzapine once-daily group. All 496 subjects who received at least 1 dose of study drug during the double-blind treatment phase had both the baseline and at least 1 post baseline PANSS total score during the double-blind treatment period and were included in the ITT analysis set.

Diagnosis and Main Criteria for Inclusion: Men and women between 18 and 65 years of age, inclusive, with a maximum BMI of 40 kg/m^2, inclusive, and diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year prior to screening and experiencing an acute exacerbation of less than 6 months duration, with a PANSS total score

at screening between 70 and 120, inclusive and at baseline of between 60 and 120, inclusive, were eligible for enrollment into the study.

Test Product, Dose and Mode of Administration, Batch No.: Study drug was provided as hard gelatin red cap red body capsules size DBAA filled with 1 or 2 tablets equivalent to 10 mg of JNJ-37822681. The batch numbers of the study drug were as follows:

- JNJ-37822681 10 mg: 08F06/F002, 09G23/G001
- JNJ-37822681 20 mg: 08F09/F003, 09G22/G002

Reference Therapy, Dose and Mode of Administration, Batch No.: Reference drug was provided as hard gelatin red cap red body capsules size DBAA filled with 1 or 2 tablets equivalent to 5 mg of olanzapine and beads or matching placebo. The batch numbers of the reference drug were as follows:

- Olanzapine 5 mg: 08C11/F318, 09G18/G010
- Olanzapine 10 mg: 08C17/F292, 09G17/G011
- Placebo: 08E23/F125

Duration of Treatment: Study drug was administered orally for up to 12 consecutive weeks. Subjects randomly assigned to 1 of the 3 dose levels of JNJ-37822681 (10, 20 or 30 mg twice-daily) took the assigned dose from Day 1 onwards. Subjects randomly assigned to olanzapine received 10 mg once-daily for 1 week and then the dose was increased to 15 mg once-daily for the remainder of their participation in the study. Subjects randomly assigned to placebo received placebo for 6 consecutive weeks and then received olanzapine, first starting on 10 mg once-daily for 1 week and then increasing to 15 mg once-daily for the remainder of their participation in the study.

Criteria for Evaluation:

Efficacy Evaluations: Efficacy was based on the change from baseline of the total PANSS score of 3 fixed doses of JNJ-37822681 compared with placebo after 6 weeks treatment. Other efficacy criteria included the PANSS subscales, the CGI-S rating scale, and the SWN scale compared with placebo at 6 weeks, and compared with olanzapine at 12 weeks. Assessment of the acute response to JNJ-37822681 relative to placebo was assessed using the changes from baseline in the NOSIE in the first 2 weeks while subjects were hospitalized.

Evaluations of Body Mass and Metabolic Markers: The body mass parameters (body weight, waist circumference) were evaluated; BMI was calculated from height and weight. A fasting plasma sample for lipid metabolism (fasting total cholesterol, triglycerides, HDL, LDL, VLDL, free fatty acids), glucose HbA_{1c}, and insulin was collected.

Pharmacokinetic Evaluations: A venous blood sample of 4 mL was collected for determination of JNJ-37822681 plasma concentrations. Population pharmacokinetic (PK) analysis of plasma concentration-time data of JNJ-37822681 was performed using nonlinear mixed-effects modeling. Data were combined with those from a selection of Phase 1 studies to support a relevant structural model; details were presented in a population pharmacokinetic/pharmacodynamic (PK/PD) analysis plan and the results are described in a separate population PK report.

Pharmacogenomic Evaluation: A pharmacogenomic blood sample (10 mL) was collected at baseline from the subjects who consented separately to an optional pharmacogenomic component of the study (where local regulations permitted).

Safety Evaluations: The primary population for evaluation of safety was all randomized subjects who received at least 1 dose of double-blind study drug. Treatment emergent adverse events, laboratory analyte values, vital sign measurements, electrocardiogram (ECG) data, physical examination, including height (screening only), body weight, and waist circumference, extrapyramidal symptoms evaluated using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS), as well as clinical symptoms using the PANSS and the CGI-S reported during the study were summarized.

Statistical Methods:

The sample size for the study was based on the assumption of a treatment difference of at least 10 points in the mean change from baseline to study endpoint (Week 12) in PANSS total score between any JNJ-37822681 dose group and placebo. The standard deviation was estimated to be 20, and the overall significance level put at 5% (ie, at 1.7% for each of the multiple comparisons of JNJ-37822681 with placebo), resulting in a power of 83%.

All randomized subjects who received at least 1 dose of study drug during the double-blind treatment phase and had both the baseline and at least 1 postbaseline PANSS total score during the double-blind treatment phase were included in the efficacy analyses. The primary endpoint in the double-blind treatment phase was the change in the total score of the PANSS from baseline to the end of the first 6 weeks of double-blind treatment.

A mixed model repeated measures (MMRM) analysis was performed on the observed change from baseline scores. The model included baseline PANSS total score and baseline body weight as covariates, with country, treatment, visit and treatment-by-visit as fixed effects. An unstructured covariance matrix was employed. The primary time point was Week 6 (Day 43). Appropriate contrasts were used to determine the estimated differences between each JNJ-37822681 dosage and placebo. Dunnett's test was used to adjust for multiple comparisons of the 3 JNJ-37822681 dosages versus placebo and the corresponding 2-sided 95% confidence intervals were presented.

RESULTS:

SUBJECT DISPOSITION AND STUDY COMPLETION/WITHDRAWAL INFORMATION

Approximately 60% of the subjects randomly assigned to treatment completed the study. The most common reasons for withdrawal from the study were lack of efficacy, withdrawal of consent, and adverse event. Lack of efficacy as a reason for withdrawal occurred at a higher rate in the placebo/olanzapine treatment group compared with the other treatment groups. The majority of early discontinuations due to lack of efficacy in the placebo/olanzapine group occurred during the first 4 weeks of treatment.

Study Completion/Withdrawal Information
(Study JNJ-37822681SCH2002: All Randomized Subjects Analysis Set)

Disposition Status Standardized Disposition Term	Placebo / Olanzapine (N=101) n (%)	JNJ-37822681 10 mg bid (N=100) n (%)	JNJ-37822681 20 mg bid (N=104) n (%)	JNJ-37822681 30 mg bid (N=100) n (%)	Olanzapine 15 mg qd (N=93) n (%)
COMPLETED	49 (49)	58 (58)	59 (57)	61 (61)	71 (76)
WITHDRAWN	52 (51)	42 (42)	45 (43)	39 (39)	22 (24)
Lack of efficacy	34 (34)	21 (21)	18 (17)	14 (14)	8 (9)
Withdrawal of consent	9 (9)	10 (10)	12 (12)	9 (9)	9 (10)
Adverse event	3 (3)	9 (9)	10 (10)	11 (11)	3 (3)
Subject choice	4 (4)	1 (1)	1 (1)	4 (4)	1 (1)
Lost to follow-up	0	0	2 (2)	1 (1)	1 (1)
Noncompliance with study drug	1 (1)	0	0	0	0
Other	1 (1)	1 (1)	2 (2)	0	0

Note: Percentages calculated with the number of subjects in each group as denominator.
Key: bid=twice daily; qd=once daily
tsub03.rtf generated by rsub61.sas, 16JUN2010 16:39

SUBJECT DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline characteristics of the ITT analysis set were consistent with the expected population based upon the study inclusion and exclusion criteria. Of the 492 subjects included in the ITT analysis set, 57% were men and the majority (82%) were white. Mean age was 39.4 years; the majority of subjects (72%) were in the age range of 26 to 50 years.

The majority of subjects (87%) had a diagnosis of paranoid schizophrenia according to DSM-IV. Mean age at first diagnosis was 27.2 years, and the mean PANSS total score was 90.5 (range 61 to 120 points). Investigators rated 50% of subject as at least markedly severe on the CGI at baseline. Most subjects (72%) had at least 3 prior hospitalizations.

The mean duration in days of the most recent hospitalization prior to participation in the double-blind treatment phase was 90.3 days. Overall, the mean duration of the most recent hospitalization was lower in subjects enrolled in the 30-mg JNJ-37822681 twice-daily and 15-mg olanzapine once-daily treatment groups compared with subjects enrolled in the placebo, 10-mg JNJ-37822681 twice-daily, and 20-mg JNJ-37822681 twice-daily treatment groups. Nearly 50% of subjects in any treatment group were hospitalized for 30 to 90 days during their most recent hospitalization.

EFFICACY RESULTS:

Using the ITT mixed model repeated measures (MMRM) analysis, treatment with all 3 doses of JNJ-37822681 (10, 20, and 30 mg twice daily) or olanzapine (15 mg once daily) showed statistically significant improvement (p values adjusted for multiplicity: <0.001) in the primary efficacy analysis, change in the PANSS total score from baseline to the end of the first 6 weeks (Day 43), compared with placebo. The least-squares adjusted mean changes from baseline to Day 43 in PANSS total score, where decreases from baseline represent improvement, were -6.4 in the placebo group, -18.4, -17.7, and -20.0 in the 10-, 20-, and 30-mg JNJ-37822681 twice-daily groups, respectively, and -22.9 in the 15-mg olanzapine once-daily group. No statistically significant country effect was found for the primary efficacy measure. The 30-mg JNJ-37822681 twice-daily treatment group showed statistically significant improvement over placebo as early as Day 3 onward ($p<0.05$, unadjusted for

multiplicity); statistically significant improvement over placebo ($p<0.05$, unadjusted for multiplicity) was reached from Day 8 onward in the 10- and 20-mg JNJ-37822681 twice-daily and 15-mg olanzapine once-daily groups.

The incidences of subjects that reached an improvement from baseline of at least 30% in PANSS total score by Day 43 were 26% for the placebo group, 50%, 48%, and 52% for the 10-, 20-, and 30- mg JNJ-37822681 twice-daily groups, respectively, and 67% for the 15-mg olanzapine once-daily group.

All 3 JNJ-37822681 twice-daily treatment groups, as well as the 15-mg olanzapine once-daily treatment group, showed statistically significant improvement from baseline up to Day 43 compared with placebo ($p<0.05$) in the PANSS subscales (positive and negative subscales and general psychopathology), in each of the Marder factors (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement and anxiety/depression), in CGI-S, and in SWN.

Compared with 15-mg olanzapine once-daily treatment, the improvements in PANSS total score, in PANSS subscales and Marder factors, and in CGI-S at Day 85 were similar for the 30-mg JNJ-37822681 twice-daily group, whereas statistically significantly less improvement was observed for the 10- and 20-mg JNJ-37822681 twice-daily treatment groups on PANSS total score, PANSS Positive and General subscales, PANSS positive symptoms, and CGI-S.

A clear dose response for efficacy was not evident; however, the highest JNJ-37822681 dose group (30 mg twice daily) showed the best response numerically of the 3 doses at 6 weeks (Day 43), compared with placebo, on both the mean change in PANSS total score and in the percentage of responders. More subjects in the placebo/olanzapine treatment group (34%) discontinued due to lack of efficacy than in the JNJ-37822681 10-mg, 20-mg and 30-mg twice-daily groups (21%, 17%, 14%, respectively), supporting the efficacy of JNJ-37822681. Withdrawal due to lack of efficacy was lowest in the 15-mg olanzapine once-daily group (9%).

SAFETY RESULTS:

Of the 496 subjects in the safety analysis set, 358 (72%) subjects experienced a treatment-emergent adverse event.

Overall Summary of Treatment-Emergent Adverse Events
(Study JNJ-37822681SCH2002: Safety Analysis Set)

	Placebo / Olanzapine (N=100) n (%)	JNJ-37822681 10 mg bid (N=99) n (%)	JNJ-37822681 20 mg bid (N=104) n (%)	JNJ-37822681 30 mg bid (N=100) n (%)	JNJ-37822681 Total (N=303) n (%)	Olanzapine 15 mg qd (N=93) n (%)
Treatment-emergent adverse event	68 (68)	65 (66)	80 (77)	77 (77)	222 (73)	68 (73)
Possibly related adverse event[a]	36 (36)	36 (36)	49 (47)	63 (63)	148 (49)	42 (45)
Serious adverse event	8 (8)	7 (7)	12 (12)	8 (8)	27 (9)	5 (5)
Adverse event leading to discontinuation of study drug	4 (4)	7 (7)	8 (8)	12 (12)	27 (9)	2 (2)

[a] Study drug relationships of possible, probable, and very likely are included in this category.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
tae10.rtf generated by rae61.sas, 16JUN2010 16:39

The most common (ie, those experienced by 10% or more of subjects) adverse events overall were insomnia and akathisia. Adverse events that were reported more frequently in subjects

treated with JNJ-37822681 across all dosing groups compared with subjects treated with placebo or olanzapine were insomnia, akathisia, somnolence, and agitation.

The incidence of (exacerbation of) schizophrenia was higher in the placebo treatment group compared with the JNJ-37822681 (overall) and olanzapine groups, as was the incidence of anxiety. Incidences of akathisia, somnolence, and tremor increased with increasing JNJ-37822681 dose.

Treatment-Emergent Adverse Events in at Least 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term
(Study JNJ-37822681SCH2002: Safety Analysis Set)

	Placebo /	---------- JNJ-37822681 ----------				Olanzapine
	Olanzapine	10 mg bid	20 mg bid	30 mg bid	Total	15 mg qd
Body System Or Organ Class	(N=100)	(N=99)	(N=104)	(N=100)	(N=303)	(N=93)
Dictionary-Derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events	68 (68)	65 (66)	80 (77)	77 (77)	222 (73)	68 (73)
Psychiatric Disorders	38 (38)	39 (39)	36 (35)	38 (38)	113 (37)	29 (31)
Insomnia	15 (15)	21 (21)	10 (10)	21 (21)	52 (17)	11 (12)
Schizophrenia	14 (14)	10 (10)	8 (8)	9 (9)	27 (9)	7 (8)
Anxiety	13 (13)	10 (10)	5 (5)	8 (8)	23 (8)	5 (5)
Agitation	4 (4)	7 (7)	6 (6)	6 (6)	19 (6)	3 (3)
Nervous System Disorders	17 (17)	20 (20)	35 (34)	49 (49)	104 (34)	25 (27)
Akathisia	5 (5)	8 (8)	10 (10)	22 (22)	40 (13)	7 (8)
Somnolence	3 (3)	2 (2)	8 (8)	11 (11)	21 (7)	6 (6)
Headache	6 (6)	5 (5)	6 (6)	6 (6)	17 (6)	4 (4)
Tremor	2 (2)	2 (2)	3 (3)	10 (10)	15 (5)	5 (5)
Gastrointestinal Disorders	8 (8)	10 (10)	15 (14)	9 (9)	34 (11)	15 (16)
Nausea	4 (4)	5 (5)	1 (1)	2 (2)	8 (3)	0

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.
tae01a.rtf generated by rae61.sas, 16JUN2010 16:39

The majority of adverse events were mild or moderate in severity across all treatment groups. Most of the adverse events that were considered severe were in the nervous system or psychiatric disorders classes. Severe adverse events experienced by more than 1 subject in any of the JNJ-37822681 dose groups were schizophrenia and akathisia.

The majority of adverse events were considered by the investigator as not related, of doubtful relationship, or possibly related to study drug. In the JNJ-37822681 groups overall, 49% of subjects experienced an adverse event considered by the investigator as at least possibly (ie, possible, probably, or very likely) related to study drug, compared with 36% and 45% in the placebo/olanzapine and olanzapine groups, respectively. Incidences of adverse events considered at least possibly (ie, possible, probably, or very likely) related increased with increasing JNJ-37822681 dose. Adverse events considered by the investigator as probably or very likely related to study drug experienced by more than 1 subject in any of the JNJ-37822681 dose groups were: insomnia, akathisia, parkinsonism, somnolence, tremor, dystonia, dry mouth, increased weight, and muscle rigidity.

No subjects died during this study. A total of 40 (8%) subjects experienced a serious adverse event during the study. Rates of serious adverse events were slightly higher in the 20-mg JNJ-37822681 dose group (12%) compared with the other treatment groups (7% and 8% in the 10- and 30-mg JNJ-37822681 groups and 8% and 5% in the placebo/olanzapine and olanzapine groups, respectively). Serious adverse events experienced by more than 1 subject in any of the JNJ-37822681 dose groups were (exacerbation of) schizophrenia and psychiatric disorder. Exacerbation of schizophrenia as a serious adverse event was experienced by fewer subjects in the JNJ-37822681 groups overall compared with either placebo/olanzapine and olanzapine, and was lower in the 10-mg JNJ-37822681 group compared with the 20- and 30-mg JNJ-37822681 groups.

A total of 33 (7%) of subjects had an adverse event that led to discontinuation of study drug. Rates of adverse events leading to study drug discontinuation were higher in the 10-, 20-, and 30-mg JNJ-37822681 dose groups (7%, 8%, and 12%, respectively) compared with the placebo/olanzapine and olanzapine groups (4% and 2%, respectively). Adverse events leading to discontinuation from study drug by more than 1 subject in any of the JNJ-37822681 dose groups were akathisia and (exacerbation of) schizophrenia.

In addition, 1 subject in the 30-mg JNJ-37822681 twice-daily group reported an adverse event of grand mal convulsion. The event was considered serious and probably related to study drug by the investigator, led to discontinuation of study drug, and was reported as a suspected unexpected serious adverse reaction (SUSAR).

There were 2 subjects who discontinued study treatment due to adverse events of prolonged QT. One subject in the 10-mg JNJ-37822681 twice-daily group had an adverse event of QTc prolongation (>500 msec), considered mild in severity and probably related to study drug by the investigator, which led to discontinuation of study drug. Another subject in the 30-mg JNJ-37822681 twice-daily group had an adverse event of mild relative QTcB prolongation greater than 60 msec compared with baseline, which was considered very likely related to study drug by the investigator and led to discontinuation of study drug. While the QTcB prolongation for this subject was greater than 60 msec compared with baseline values, it was similar to that observed at screening.

In the 20-mg JNJ-37822681 twice-daily group, when examining the UKU side effects, there was a higher incidence of severe erectile dysfunction, decreased sexual desire, and premature or delayed ejaculation or orgasmic dysfunction compared with the other treatment groups. These events were likely spurious as they were not reported in spontaneous adverse event reporting.

Incidences of EPS-related adverse events were similar between the placebo/olanzapine, olanzapine, and 10-mg JNJ-37822681 treatment groups, whereas the rates of EPS-related adverse events were higher in subjects treated with the 20 and 30 mg JNJ-37822681. A dose-related pattern in the number and onset of akathisia events and other EPS-related adverse events was observed in the JNJ-37822681 treatment groups. With the exception of 2 reports of akathisia in the 30-mg JNJ-37822681 twice-daily group, all adverse events of akathisia were mild or moderate in severity. Only 2 (1%) subjects treated with 30 mg JNJ-37822681 twice daily and 1 (1%) subject on olanzapine once daily reported glucose-related adverse events. More subjects in the olanzapine group reported potentially prolactin-related adverse events than in the other treatment groups. None of the subjects in the 10-mg JNJ-37822681 treatment group reported prolactin-related adverse events.

Overall, changes in vital signs and ECG parameters were similar between the treatment groups. A higher number of subjects in the 30-mg JNJ-37822681 twice-daily group had abnormally low heart rates (≤50 beats per minute [bpm]) compared with the other treatment groups. Abnormal decreases in heart rates were less apparent when assessed as pulse rates in vital signs. In addition to heart rate ≤50 bpm, the criteria for abnormal pulse also include change from baseline of at least 15 bpm, and are therefore more restrictive.

A review of the clinical laboratory data did not reveal any significant safety signals in the JNJ-37822681 groups. Average prolactin levels on Day 43 were similar in the placebo/olanzapine and 10-mg JNJ-37822681 groups, but were numerically higher in the 20- and 30-mg JNJ-37822681 and olanzapine treatment groups. Plasma metabolic results at Week 12 showed favorable trends for JNJ-37822681 compared with olanzapine for fasting triglycerides, glucose, insulin, HbA_{1C}, HDL- and VLDL-cholesterol. For these same measures at Week 6, the 10-. 20-, and 30-mg JNJ-37822681 twice-daily doses did not differ significantly from placebo. Statistically significant increases in mean total cholesterol were observed at Day 43 compared with placebo for the 20- and 30-mg JNJ-37822681 twice-daily and 15-mg olanzapine once-daily treatment groups, but not for the 10-mg JNJ-37822681 twice-daily group. The incidence of subjects who developed fasting glucose levels >126 mg/dL during the study (but had normal levels, <100 mg/dL, at baseline) was higher in the olanzapine group (20%) compared with the placebo/olanzapine and 10-, 20-, and 30-mg JNJ-37822681 groups (≤8%).

For all 3 JNJ-37822681 dose groups, the changes in BMI, body weight, and waist circumference from baseline to study endpoint (Week 12) were statistically significantly less than for the olanzapine-treated group. A higher percentage of subjects with normal weight (defined as 18.5≤ BMI <25 kg/mL^2) at baseline showed a greater than 7% increase in weight at Day 85 in the 15-mg once-daily olanzapine treatment group (37%) compared with the placebo/olanzapine (8.0%) and JNJ-37822681 twice-daily treatment groups (8.5%, 6.7%, and 7.1%, for the 10-, 20-, and 30-mg groups, respectively). Subjects who experienced weight increases on JNJ-37822681 were more likely to be underweight (BMI <18.5) at baseline.

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

CONCLUSIONS:

JNJ-37822681 was effective across the 3 doses tested (10, 20, and 30 mg twice daily), and showed superiority to placebo in the changes from baseline in the PANSS total score, PANSS subscales, Marder factors, response-rate, and CGI-S after 6 weeks of treatment.

At Week 12, improvements in PANSS total score, in PANSS subscales and Marder factors, and in CGI-S were similar for the 30-mg JNJ-37822681 twice-daily group, whereas statistically significantly less improvement was observed for the 10- and 20-mg JNJ-37822681 twice-daily treatment groups on PANSS total score, PANSS positive and general subscales, PANSS positive symptoms, and CGI-S.

A clear dose response for efficacy was not evident; efficacy results with the 3 doses of JNJ-37822681 overlapped. Onset of efficacy was early (Day 3 for the 30-mg JNJ-37822681 twice-daily dose), and evident for all doses by Day 8.

JNJ-37822681 was generally safe and well tolerated, and had a safety profile consistent with that predicted by the mechanism of action. Adverse events that were reported more frequently in subjects treated with JNJ-37822681 across all dosing groups compared with subjects treated with placebo or olanzapine were insomnia, akathisia, somnolence, agitation, and

tremor. Changes in vital signs and ECG parameters were similar across the placebo/olanzapine and JNJ-37822681 treatment groups. Review of the clinical laboratory data did not reveal any significant safety signals.

The safety profile of JNJ-37822681 was favorable overall compared with olanzapine. Plasma metabolic results at Day 85 showed favorable trends for JNJ-37822681 compared with olanzapine for fasting triglycerides, glucose, insulin, HbA_{1C}, HDL- and VLDL-cholesterol. The incidence of subjects who developed fasting glucose levels >126 mg/dL during the study (but had normal levels, <100 mg/dL, at baseline) was higher in the olanzapine group compared with the the placebo/olanzapine and 10-, 20-, and 30-mg JNJ-37822681 groups. Changes in body weight, BMI, and waist circumference from baseline to Day 85 were less for all the JNJ-37822681 twice-daily groups compared with the 15-mg olanzapine once-daily group. Those subjects who experienced weight increases on JNJ-37822681 were more likely to be underweight (BMI <18.5) at baseline. Moreover, a higher percentage of subjects with normal weight (defined as $18.5 \leq$ BMI <25 kg/mL^2) at baseline showed a greater than 7% increase in weight at Day 85 in the 15-mg once-daily olanzapine treatment group compared with the placebo/olanzapine and JNJ-37822681 twice-daily treatment groups.

While the lowest effective dose for JNJ-37822681 has not yet been defined, the safety profile of the 10-mg JNJ-37822681 twice-daily dose suggests that this dose may have the most positive benefit/risk ratio (ie, minimal to no weight gain, with minimal metabolic and EPS liability, and without prolactin elevating effects) compared with the 20- and 30-mg JNJ-37822681 twice-daily doses.