Johnson & Johnson Pharmaceutical Research & Development

Clinical Study Synoptic Report

A Double-Blind, Multiple-Dose Titration Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Once-Daily and Twice-Daily Doses of JNJ-37822681 in Male and Female Patients With Stable Schizophrenia

Protocol 37822681SCH2003; Phase 2a

JNJ-37822681

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EudraCT Number: 2007-007669-20

COORDINATING INVESTIGATOR: Prof. Winterer; Germany

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Luc Van Nueten, M.D.

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Jyoti Arora
Kinapse Ltd
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Name of Finished Product	Not Applicable
Name of Active Ingredient	JNJ-37822681

Protocol No.: 37822681SCH2003

Title of Study: A Double-Blind, Multiple-Dose Titration Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Once-Daily and Twice-Daily Doses of JNJ-37822681 in Male and Female Patients With Stable Schizophrenia

EudraCT Number: 2007-007669-20

Coordinating Investigator: Prof. Winterer; Germany.

Publication (Reference): None

Study Period: 27 June 2008 to 18 December 2008; database lock date: 13 January 2009

Phase of Development: 2a

OBJECTIVES:

The primary objective was to investigate the safety and tolerability of JNJ-37822681 administered once daily or twice daily following a dose titration in men and women with stable schizophrenia.

The secondary objectives of this study were:

- To investigate the plasma pharmacokinetic (PK) profile of JNJ-37822681 administered once daily or twice daily in men and women with stable schizophrenia;
- To investigate the effect of JNJ-37822681 on plasma prolactin (PRL) levels;
- To investigate the occupancy of striatal dopamine D_2 receptors of JNJ-37822681 following multiple-dose administration in relation to the plasma PK profile using carbon 11 [^{11}C] -raclopride positron emission tomography (PET).

METHODS:

- This was a multi-center, double-blind, multiple-dose titration study in men and women with stable schizophrenia to investigate the safety and tolerability of JNJ-37822681 at doses up to 80 mg per day, given either once daily or twice daily. The highest dose of 80 mg was chosen as this was predicted to result in saturation or near saturation of the

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striatal D2 dopamine receptors and therefore provide guidance on the tolerability of exposures at the upper end of the anticipated clinical dose range.

- The study consisted of a screening examination, a washout period (if appropriate), a 14-day double-blind treatment period, an optional 2-day down-titration period, an optional 3-day observation period, and a follow-up examination between 7 and 14 days after last dose administration.
- During the screening period, T1 weighted magnetic resonance imaging (MRI) of the brain was obtained to provide anatomic image volumes for co-registration with the PET image volumes for image data analysis. Eligible subjects on antipsychotic medication entered a minimally 1-day and maximally 5-days washout period to taper off their current antipsychotic medication. The washout period was done under daily psychiatric surveillance (phone call, and visit).
- Subjects were randomly assigned to treatment with ascending dose levels of JNJ-37822681 once daily and twice daily. Doses of study drug were increased gradually by a maximum of 10 mg per day from Day 4 to Day 10 inclusive, upon the decision of the Investigator, guided by the individual's tolerability profile, according to the schedule in Table 1.
- Subjects who were randomly assigned to once-daily treatment received JNJ-37822681 in the morning and then received a placebo dose in the evening so that all subjects were dosed twice during each day.

Table 1: Dose Escalation
Study 37822681SCH2003

Study Day	Once Daily (mg)	Twice Daily (mg)
1	20	10 + 10
2	20	10 + 10
3	20	10 + 10
4	30	20 + 10
5	40	20 + 20
6	50	30 + 20
7	60	30 + 30
8	70	40 + 30
9	80	40 + 40
10	80	40 + 40
11	80	40 + 40
12	80	40 + 40
13	80	40 + 40
14	80	40 + 40
15*	60	30 + 30
16*	40	20 + 20

*optional down-titration before re-starting normal antipsychotic drug treatment
Cross reference: Appendix 1.1

- All subjects started an up to 10-days titration period as inpatients, with the first 3 days being at the starting dose (no increase). Upon reaching the maximal tolerable dose level (or 80 mg once daily), no further dose escalations were made and dosing was continued up to Day 14. Dosing was stable from Day 10 to Day 14.
- At the end of the 14-day double-blind treatment period, treatment with JNJ-37822681 was discontinued and subjects resumed their previous antipsychotic treatment 24 hours after the last dose administration. Reinstatement of the subject's previous antipsychotic treatment was guided and supervised by a psychiatrist over a 72 hour observation period.

- The Investigator had the option of down titrating the dose of JNJ-37822681 on Day 15 and Day 16 before starting the subject's previous antipsychotic treatment.
- Subjects were discharged from the clinical center after the last PK sample was taken and after successful reinstatement of their previous antipsychotic medication (between Day 15 and Day 20).
- Throughout the study, regular assessments were made to investigate the safety and tolerability of JNJ-37822681. In addition, blood samples were collected for the measurement of PRL and JNJ-37822681 plasma concentrations.
- [^{11}C]-raclopride PET scans were available at or near 2 of the study sites. Up to 12 eligible subjects at those sites were to be requested to undergo [^{11}C]-raclopride PET scans after receiving JNJ-37822681 for at least 10 days, and on their highest tolerated dose or highest dose per protocol for at least 3 days. Subjects were transported under medical supervision to the PET Center to undergo the scan approximately 2 hours post morning dose (the estimated time of peak plasma concentration).
- The original protocol was issued on 20 February 2008, Protocol Amendment NED-1 SS-1 was issued on 18 March 2008 and Protocol Amendment INT-1 was issued on 23 April 2008. The following changes were introduced:
  - During the screening period a T1 weighted MRI of the brain was taken to provide anatomic image volumes for co-registration with the PET image volumes for image data analysis.
  - Up to 12 subjects were to undergo [^{11}C]-raclopride PET scans. In these subjects, 200 MBq (range: ±10%) [^{11}C]-raclopride was coadministered as a slow bolus intravenous infusion 2 hours after the morning dose of JNJ-37822681 and was followed by a saline flush
  - Dosing time of JNJ-37822681 or placebo was adjusted according to the scheduling of the [^{11}C]-raclopride scan at the PET center. Morning doses were administered at the same time on Days 1 to 10, evening doses were administered 12 hours later. On Days 11 to 14, a dosing time window of ±3 hours was allowed.

Number of Subjects (planned and analyzed):

- Planned: A minimum of 30 and maximum of 36 subjects were to be enrolled in order to ensure at least 24 subjects completed the study. At least 12 subjects were to undergo [^{11}C]-raclopride PET scans.
- Analyzed: In total, 33 subjects were enrolled in this study and analyzed for safety. Eighteen subjects had complete profiles and were analyzed for PK parameters. Post-baseline PET scans were obtained in 3 subjects.

Diagnosis and Main Criteria for Inclusion:

- Subjects were men and women between 20 and 55 years of age (inclusive), with a body mass index (BMI) between 18 and 35 kg/m^2, (inclusive). Subjects who had a PET scan were between 20 and 45 years, inclusive.
- Women were either postmenopausal (amenorrhea for at least 12 months and follicle stimulating hormone levels of >40 MIU/mL at screening), or surgically sterile, (had a hysterectomy or bilateral oophorectomy, tubal ligation, or were otherwise incapable of pregnancy).
- Subjects had a Positive and Negative Syndrome Scale (PANSS) score at screening <70.

- Subjects met Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for schizophrenia and had a known history of schizophrenia of at least 12 months referred by a psychiatrist.
- Subjects with schizophrenia were stably treated for at least 6 months with antipsychotic monotherapy (≤200 mg per day chlorpromazine equivalent dose) or stable for at least 3 months without drug therapy; subjects who received a second antipsychotic at doses lesser than recommended for antipsychotic efficacy could participate, provided the second antipsychotic was discontinued at least 2 weeks prior to the first study administration of study drug.

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

- The study drug provided as eq. 10 mg hard gelatin red cap red body capsules size DBAA filled with 1 tablet JNJ-37822681 and beads. Batch Number: 08B01/F002.
- A physical description of [^{11}C] raclopride, and details on its synthesis are provided in the Investigational Medicinal Product Dossier (IMPD SCH2003).

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

- Placebo was provided as matching hard gelatin red cap red body capsules size DBAA. Batch Number: 06L06/F125.

Duration of Treatment:

- All subjects received up to 40 mg JNJ-37822681 twice daily or 80 mg JNJ-37822681 once daily for 14 consecutive days from Day 1 to Day 14. The total study duration for an individual subject was approximately 8 weeks.

Criteria for Evaluation:

Pharmacokinetic Evaluations:

- Venous blood samples of 4 mL were collected for determination of JNJ-37822681 plasma concentrations at the timepoints specified in the Time and Events Schedule of the protocol (Appendix 1.1).
- Plasma samples were analyzed to determine concentrations of JNJ-37822681 using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.
- Some plasma samples were analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples were stored for future analysis of the metabolite profile.
- Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters of JNJ-37822681 were estimated (as applicable after the first dose on Day 1 or the last dose on Day 14 or both):
  - C_{max} peak plasma concentration, determined by visual inspection of the data
  - $C_{predose}$ predose plasma concentration (intermittent days and predose Day 14)
  - C_{avg} average plasma concentration at steady state, calculated as AUC_{τ}/τ
  - C_{min} minimum observed plasma concentration during the dosing interval (τ) at steady state
  - t_{max} time to reach the peak plasma concentration, determined by visual inspection of the data

- $AUC_{12h/24h}$ area under the plasma concentration-time curve from 0 to 12 or from 0 to 24 hours postdose on Day 1 and Day 14, calculated by trapezoidal summation
- AUC_{τ} area under the plasma concentration-time curve from 0 to τ hours post dosing at steady state, calculated by trapezoidal summation (time τ is the dosing interval)

Pharmacodynamic Evaluations:

- Venous blood samples were collected at specified timepoints during the study for the measurement of PRL plasma concentrations.
- The [^{11}C]-raclopride PET scans were completed as described in Sections 5 and 9.1 of the protocol (Appendix 1.1), and in the PET Manual.

Safety Evaluations:

- Adverse events and concomitant medications were reported throughout the study.
- Blood and urine samples for clinical laboratory tests (including thyroid stimulating hormone [TSH] measurements) were taken, and a 12-lead electrocardiogram (ECG), vital signs, and physical examinations were performed at timepoints specified in the Time and Events Schedule of the protocol (Appendix 1.1).
- Extra pyramidal symptoms (EPS) were 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 Clinical Global Impression – Schizophrenia (CGI-SCH) and PANSS at timepoints specified in the Time and Events Schedule of the protocol (Appendix 1.1).
- All clinically significant abnormalities persisting at the end of the study were followed and reported throughout the study.

Statistical Methods:

- Sample size was not determined on statistical considerations, but was regarded as sufficient for exploring the tolerability of a total daily dose of 80 mg and to provide an indication of the relative tolerability of single (once-daily) versus divided (twice-daily) dose regimen.
- Twenty four subjects completing the study were judged sufficient to yield relevant safety and tolerability information.
- Descriptive statistics were calculated for the JNJ-37822681 plasma concentrations at each sampling time and for all PK parameters of JNJ-37822681. Depending on a number of different possible dose levels reached by individual subjects on Day 14, dose proportionality was to be explored graphically.
- The relationship between drug and PRL concentrations was to be evaluated graphically. Pharmacokinetic parameters and PRL concentrations were to be included in a cross study comparison, using population PK and PK/ pharmacodynamic (PD) approaches.
- Analyses of PET measurement results to calculate the percentage occupancy in the region of interest were performed by Abiant Inc. The percent occupancy was estimated by comparing the binding volume of the tracer in subjects to an average baseline value from a reference population.

- The safety analysis of all subjects randomized to JNJ-37822681 included the incidence of adverse events; actual data and changes in blood pressure, pulse rate, laboratory safety data, 12-lead ECG, physical examination data, EPS scales and clinical symptom scales from baseline to all postdose assessments.

RESULTS:

- Thirty-three subjects with schizophrenia were randomly assigned to treatment in this study. Twenty-nine subjects completed the study and 4 discontinued (Table 2). Of the 4 discontinued subjects, 2 were discontinued due to adverse events, 1 due to subject's choice, and 1 due to a reason categorized as 'other'. More information on the subjects who discontinued due to adverse events and the subjects who discontinued due to a reason categorized as other are provided below under Safety Results. All 4 subjects that discontinued were in the 40-mg JNJ-37822681 twice-daily treatment group; all 15 subjects in the 80-mg JNJ-37822681 once-daily treatment group completed the study.

Table 2: Study Completion/Withdrawal Information
(Study 37822681SCH2003: Safety Analysis Set)

Subject Completed Treatment/trial Reason for Withdrawal/termination	40mg bid (N=18) n (%)	80mg od (N=15) n (%)	Total (N=33) n (%)
Completed	14 (78)	15 (100)	29 (88)
Withdrawn	4 (22)	0	4 (12)
Adverse Event	2 (11)	0	2 (6)
Other	1 (6)	0	1 (3)
Subject Choice	1 (6)	0	1 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross reference: Attachment 1.1
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- Demographic and other baseline characteristics are given in Table 3. The majority of subjects were white (32 [97%]) and men (30 [91%]). The mean age was 36.5 years (range 21 to 54 years) and the mean BMI was 27.4 kg/m^2 (range 20 to 34 kg/m^2).
- Mean PANSS scores at baseline (Day -1) were 52.61 and 51.80 for the 40-mg JNJ-37822681 twice-daily and 80-mg JNJ-37822681 once-daily treatment groups, respectively (Attachment 7.5).
- Further information on time since diagnosis of schizophrenia and antipsychotic treatment for each subject is provided in Attachments 1.4 and 1.5.

Table 3: Demographic and Other Baseline Characteristics
(Study37822681SCH2003: Safety Analysis Set)

	---- 40mg bid --- (N=18)	---- 80mg od ---- (N=15)	----- Total ----- (N=33)
Age (years)			
N	18	15	33
Mean (SD)	34.0 (9.93)	39.5 (9.83)	36.5 (10.12)
Median	33.5	38.0	36.0
Range	(21;54)	(22;54)	(21;54)
Sex, n (%)			
N	18	15	33
Male	16 (89)	14 (93)	30 (91)
Female	2 (11)	1 (7)	3 (9)
Race, n (%)			
N	18	15	33
White	18 (100)	14 (93)	32 (97)
Other	0	1 (7)	1 (3)
Weight (kg)			
N	18	15	33
Mean (SD)	86.4 (14.08)	86.7 (12.82)	86.6 (13.32)
Median	85.0	88.0	85.0
Range	(66;112)	(64;111)	(64;112)
Height (cm)			
N	18	15	33
Mean (SD)	177.2 (7.64)	178.3 (8.90)	177.7 (8.12)
Median	177.8	178.0	178.0
Range	(164;194)	(160;197)	(160;197)
Body Mass Index (kg/m^2) [a]			
N	18	15	33
Mean (SD)	27.5 (3.71)	27.2 (2.99)	27.4 (3.35)
Median	27.8	27.6	27.6
Range	(20;34)	(23;32)	(20;34)

[a]The parameter Body Mass Index is derived from weight and height
Cross reference: Attachment 1.2
tsub01.rtf generated by rsub51.sas.

- The maximum dose received is summarized in Table 4. Study drug administration information for each subject is provided in Attachment 1.3.

Table 4: Maximum Dose Received by Regimen
(Study37822681SCH2003: Safety Analysis Set)

	20mg (n=1)	40mg (n=1)	50mg (n=1)	60mg (n=1)	70mg (n=4)	80mg (n=25)	Total (n=33)
40mg bid	1				3	14	18
80mg od		1	1	1	1	11	15

- The majority of subjects (25 of 33 subjects enrolled in the study) received a maximum daily dose of 80 mg JNJ-37822681, administered either as 40 mg twice daily or 80 mg once daily.
- Of the 18 subjects randomly assigned to receive a JNJ-37822681 dose titration from 10 mg to 40 mg twice daily over 14 days, 4 subjects did not titrate up to the full dose. One of these subjects (071007 [who was discontinued on Day 2 due to an adverse event, see the subject narrative below]) received a maximum daily dose of 20 mg, and 3 subjects (491003, 421003 [who was discontinued on Day 9 due to suspected Brugada syndrome, see the subject narrative below], and 071004 [who was discontinued on Day 9 due to an adverse event, see the subject narrative below]) received a maximum daily dose of 70 mg. In addition, 2 subjects titrated up to 40 mg twice daily, but received the full dose for only 1 day: Subject 3018 titrated up to 40 mg twice daily on Day 9, but was reduced to a

maximum daily dose of 70 mg on Days 10 to 14, and Subject 7002 titrated up to 40 mg twice daily on Day 11, but was reduced to a maximum daily dose of 70 mg on Days 12 to 14.

- Of the 15 subjects randomly assigned to receive a dose titration of JNJ-37822681 from 20 mg to 80 mg once daily, 4 subjects did not titrate up to the full dose. One subject each received a maximum daily dose of 40 mg (461002), 50 mg (3015), 60 mg (492009), or 70 mg (071010); none of these subjects were discontinued due to an adverse event. In addition, Subject 492011 titrated up to 80 mg once daily on Day 9, but was reduced to a maximum daily dose of 70 mg on Days 10 to 14.

PHARMACOKINETIC RESULTS:

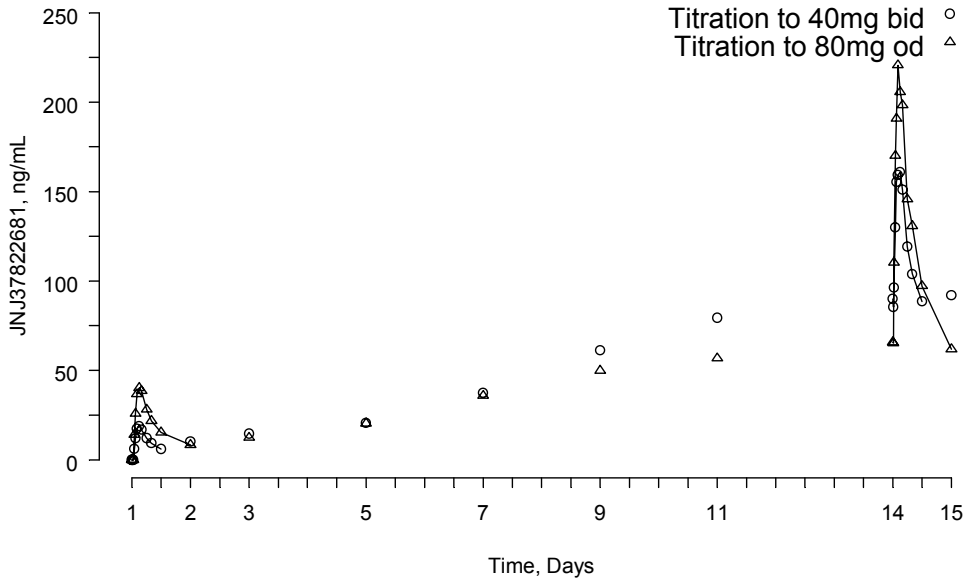
Data Sets Analyzed:

- The PK analysis set after twice-daily administration of JNJ-37822681, following a dose titration from 10 mg twice daily to 40 mg twice daily, included 18 and 12 subjects with complete profiles and PK parameters calculated on Days 1 and 14, respectively. After once-daily administration of JNJ-37822681, following a dose titration from 20 mg once daily to 80 mg once daily, the PK analysis set included 15 and 10 subjects with complete profiles and PK parameters calculated on Days 1 and 14, respectively. A total of 912 samples were collected and analyzed for JNJ-37822681 and 807 plasma concentrations were used for the descriptive statistics.
- When subjects deviated from the assigned dosing regimen, the corresponding samples were excluded from the descriptive statistics and the PK parameter calculation.
- To investigate the effect of JNJ-37822681 on plasma PRL levels, only PRL data from subjects that were included in the PK analysis set, were used in the PK/Pharmacodynamic (PD) evaluation.

Pharmacokinetic Results:

- Blood sampling times relative to JNJ-37822681 administration are provided in Attachment 2.1.
- Individual plasma concentrations, including descriptive statistics of JNJ-37822681, are provided in Attachment 2.2.
- Linear and semi-logarithmic individual, mean and median plasma concentration-time profiles of JNJ-37822681 are provided in Attachments 2.4, 2.5 and 2.6. Linear and semi-logarithmic overlay of the plasma concentration-time profiles of JNJ-37822681 per day and per treatment are provided in Attachment 2.7.
- JNJ-37822681 administered as 80 mg once daily or 40 mg twice daily was rapidly absorbed in subjects with median peak concentrations reaching at 3 hours after dosing on Day 1 and at 2 hours after dosing on Day 14 (Figure 1 and Table 5).
- Mean plasma concentration-time profiles of JNJ-37822681 when administered orally in doses up to 40 mg twice daily and 80 mg once daily are shown in Figure 1 below.

Figure 1: Mean Plasma Concentration-Time Profiles of JNJ-37822681 When Administered Orally in Doses up to 40 mg Twice Daily and 80 mg Once Daily.



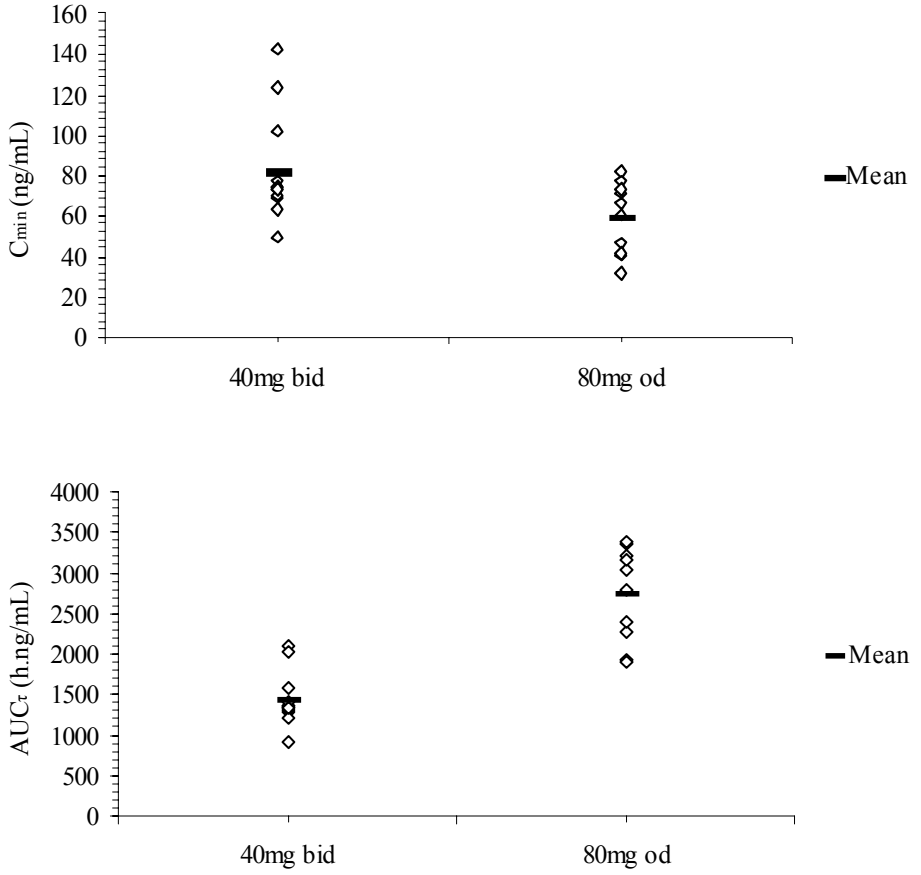
- An overview of the descriptive statistics for the main plasma PK parameters, on Day 1 and Day 14 is provided in Table 5 (Attachment 2.3).
- JNJ-37822681 administered once daily versus twice daily provided higher C_{max} to $C_{predose}$ ratios. On Day 14, the mean C_{max} to $C_{predose}$ ratio observed was approximately 2:1 for the 40-mg twice-daily regimen and 4:1 for the 80-mg once-daily regimen, reflecting a lower fluctuation with the twice-daily dosing regimen (Table 5 and Figure 2).

Table 5: Descriptive Statistics of the Main PK Parameters of JNJ-37822681 When Administered Orally in Doses up to 40 mg Twice Daily and 80 mg Once Daily

PK parameter	Dosing regimen			
	n	Titration from 10 to 40 mg bid	n	Titration from 20 to 80 mg once daily
Day 1				
C_{max} (ng/mL)	18	21.6 ± 7.20	15	46.1 ± 12.7
t_{max} (h)[a]	18	3.00 (0.50 – 6.00)	15	3.00 (1.00 – 6.00)
$AUC_{0\text{-}12h}$ (ng.h/mL)	18	132 ± 30.3	15	440 ± 118[b]
Day 14				
$C_{predose}$ (ng/mL)	12	90.0 ± 27.0	10	65.9 ± 22.7
C_{max} (ng/mL)	12	173 ± 32.7	10	247 ± 50.6
C_{avg} (ng/mL)	12	121 ± 28.0	10	114 ± 24.0
C_{min} (ng/mL)	12	82.4 ± 26.5	10	58.9 ± 17.6
t_{max} (h)	12	2.00 (1.00 – 4.00)	10	2.00 (0.50 – 4.00)
AUC_{τ} (ng.h/mL)[c]	12	1439 ± 329	10	2742 ± 571

[a] Median values (Min - Max).
[b] $AUC_{0\text{-}24h}$.
[c] $AUCt_{\tau}$, τ equals 12 hours and 24 hours for the bid and once-daily regimens, respectively.
Cross reference: Attachment 2.3

Figure 2: Main Pharmacokinetic Parameters on Day 14 of JNJ-37822681 When Administered Orally in Doses up to 40 mg Twice Daily and 80 mg Once Daily



Cross Reference: Attachment 2.8

- Future population PK analysis will further investigate the PK of JNJ-37822681 in studies conducted in subjects with schizophrenia. The data from this analysis will be reported separately in a population PK report.

RECEPTOR OCCUPANCY RESULTS

Stratial Dopamine D2 Receptor Occupancy (PET)

- Post-baseline [^{11}C]-raclopride PET scans were obtained in 3 subjects at different scheduled timepoints, ie 2 to 3 hours after twice-daily dosing on Day 13 (Subject 461003; 40 mg twice daily) and 2 to 3 hours after once-daily dosing on Day 12 (Subjects 321001 and 461002, 80 mg and 30 mg once daily, respectively).
- Several PD models were tested to correlate plasma concentrations to central D_2-occupancy. A sigmoid E_{max} model with an E_{max} fixed to 100% and with $OC_{50\%}$ (plasma concentration of JNJ-37822681 at which 50% of striatal D_2-receptor are occupied) and Hill coefficient estimated best described the data and resulted in $OC_{50\%}$ of 29.3 ng/mL (CV%, 5.3) and a Hill coefficient of 0.862 (CV%, 5.3).

Prolactin:

- Only 2 women received study medication in the study, one in each dose group, therefore, it was not possible to summarize prolactin by sex. Means and mean changes over time in PRL results obtained from men enrolled in the study are provided in Attachment 2.10; individual prolactin results from each subject are provided in Attachment 2.11.
- On Day 14, transient increases in mean plasma PRL levels above the normal limit (reference range: 0 to 934.8 pmol/mL) were observed from 1 to 6 hours after 40 mg twice-daily dosing (up to 1,778.3 pmol/mL) and after 80 mg once-daily dosing (up to 2,075.7 pmol/mL) (Attachment 2.10).
- The mean maximum PRL concentrations were 2.6 (40 mg twice daily) to 1.7 (80 mg once daily) times higher on Day 14 compared to Day 1.
- Hysteresis shaped curves were present in most of the subjects following administration of JNJ-37822681 as once daily or twice daily on Day 1 and Day 14 (Attachment 2.11). Overall, there was a good temporal relationship between the plasma PRL concentrations and the JNJ-37822681 plasma concentrations.

SAFETY RESULTS:

Adverse Events:

- All 33 enrolled subjects were included in the safety analysis.
- The by-subject listing of all adverse events reported during this study is provided in Attachment 3.1. Thirty-two (97%) subjects experienced 1 or more adverse events during this study.
- As was discussed above, 4 subjects in each treatment group did not titrate up to the full dose. Three of the 4 subjects randomly assigned to receive a JNJ-37822681 dose titration from 10 mg to 40 mg twice daily over 14 days who did not titrate up to the full dose were discontinued due to adverse events or suspected Brugada syndrome (see below for further discussion of these subjects). None of the subjects randomly assigned to receive JNJ-37822681 dose titrations of JNJ-37822681 from 20 mg to 80 mg once daily discontinued from the study due to an adverse event. The actual dose of study drug the subject received at the time of each adverse event is indicated in Attachment 3.1.
- Overall the most frequently-reported adverse events by system organ class were psychiatric disorders, nervous system disorders, gastrointestinal disorders along with general disorders, and administration sites. The incidences of psychiatric and nervous system adverse events were similar in the JNJ-37822681 40-mg twice-daily and 80-mg once-daily treatment groups. More subjects reported gastrointestinal disorders in the 40-mg JNJ-37822681 twice-daily group compared with the 80-mg once-daily group. (Table 6).
- The adverse events (preferred term) reported by 5 or more subjects treated with JNJ-37822681 were: sleep disorder, fatigue, akathisia, tachycardia, headache, tremor, diarrhea, musculoskeletal stiffness, increased diastolic blood pressure and orthostatic hypotension (Table 6).
- The incidence of fatigue was higher in subjects randomized to the JNJ-37822681 40-mg twice-daily group compared to the 80-mg JNJ-37822681 once-daily group (Table 6).

Table 6: Incidence of Treatment-Emergent Adverse Events Occurring in 2 or More Subjects by Body System and Preferred Term
(Study37822681SCH2003: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	40 mg bid (N=18) n (%)	80 mg od (N=15) n (%)	Total (N=33) n (%)
Total no. subjects with adverse events	17 (94)	15 (100)	32 (97)
Psychiatric disorders	12 (67)	11 (73)	23 (70)
Sleep disorder	6 (33)	5 (33)	11 (33)
Insomnia	2 (11)	2 (13)	4 (12)
Abnormal dreams	2 (11)	1 (7)	3 (9)
Anxiety	1 (6)	2 (13)	3 (9)
Nightmare	2 (11)	1 (7)	3 (9)
Agitation	0	2 (13)	2 (6)
Dyssomnia	2 (11)	0	2 (6)
Tension	2 (11)	0	2 (6)
Nervous system disorders	9 (50)	9 (60)	18 (55)
Akathisia	4 (22)	3 (20)	7 (21)
Headache	4 (22)	2 (13)	6 (18)
Tremor	2 (11)	3 (20)	5 (15)
Gait disturbance	0	2 (13)	2 (6)
Gastrointestinal disorders	9 (50)	3 (20)	12 (36)
Diarrhoea	3 (17)	2 (13)	5 (15)
Salivary hypersecretion	2 (11)	1 (7)	3 (9)
Dry mouth	2 (11)	0	2 (6)
Nausea	1 (6)	1 (7)	2 (6)
Vomiting	1 (6)	1 (7)	2 (6)
General disorders and administration site conditions	8 (44)	4 (27)	12 (36)
Fatigue	7 (39)	4 (27)	11 (33)
Musculoskeletal and connective tissue disorders	3 (17)	6 (40)	9 (27)
Musculoskeletal stiffness	2 (11)	3 (20)	5 (15)
Muscular weakness	0	3 (20)	3 (9)
Myalgia	0	2 (13)	2 (6)
Investigations	5 (28)	3 (20)	8 (24)
Blood pressure diastolic increased	4 (22)	1 (7)	5 (15)
Blood pressure systolic increased	2 (11)	0	2 (6)
Electrocardiogram QT prolonged	0	2 (13)	2 (6)
Cardiac disorders	4 (22)	3 (20)	7 (21)
Tachycardia	4 (22)	3 (20)	7 (21)
Bundle branch block	0	2 (13)	2 (6)
Vascular disorders	4 (22)	3 (20)	7 (21)
Orthostatic hypotension	2 (11)	3 (20)	5 (15)
Hypotension	2 (11)	0	2 (6)
Infections and infestations	5 (28)	0	5 (15)
Nasopharyngitis	4 (22)	0	4 (12)
Skin and subcutaneous tissue disorders	2 (11)	2 (13)	4 (12)
Hyperhidrosis	2 (11)	0	2 (6)

Note: Incidence is based on the number of subjects, not the number of events
Cross reference: Attachment 3.1
rae51_t3.rtf generated by rae51.sas.

- There were no deaths in this study.
- A total of 3 subjects experienced serious adverse events (Attachment 3.2) and 2 subjects were discontinued from study medication due to adverse events (Attachment 3.3):
  - 2 subjects (492007 and 071003) randomized to receive 80 mg JNJ 37822681 once daily experienced worsening of symptoms of schizophrenia (considered a serious adverse event) following treatment during the follow up period. These subjects required rehospitalization to stabilize their treatment.
  - 1 subject (071004) randomized to receive 40 mg JNJ-37822681 twice daily had serious adverse events of moderate increased aspartate aminotransferase (AST) and severe increased blood creatine phosphokinase (CPK) that also led to discontinuation of study medication.
  - 1 subject (071007) randomized to 40 mg JNJ-37822681 twice daily, was discontinued from study medication at the request of the Sponsor due to the adverse event of hypercalcemia identified in the screening and baseline labs.
- In addition, 1 subject (421003), treated with 40 mg JNJ 37822681 twice daily, was discontinued from study medication by the Investigator, after consultation with the Sponsor, due to a reason categorized as other: suspected Brugada syndrome observed in the predose ECG on Day 1, which was not reported as an adverse event as it was present at screening. Dosing occurred in this subject for 8 days until the finding was provided to the Investigator from a central ECG reader. (Attachment 1.1).
- Narratives for the subjects who had serious adverse events or discontinued due to an adverse event, as well as for the subject who was discontinued due to Brugada syndrome, are provided below.
  - **Subject 492007 (serious adverse event: psychotic disorder):** This 46-year-old white man with a history of schizophrenia since 1994 was randomly assigned to receive dose titrations of JNJ-37822681 from 20 mg to 80 mg once daily over 14 days. The subject ended his previous therapy of 3 mg oral risperdal once daily on Day –2. The subject received JNJ-37822681 for 14 days, with the maximum daily dose of 80 mg achieved on Days 9 to 14. On Day 5, the subject experienced mild agitation, which resolved after treatment with 1 mg lorazepam on Day 23. On Day 7, the subject experienced recurrence of mild agitation, which resolved after treatment with 1 mg lorazepam 4 times daily on the same day. The Investigator considered both events of agitation as not related to the study drug administration. On the same day (Day 7), the subject experienced mild sleep disorder, which was treated with 7.5 mg zopiclone. The Investigator considered the event of sleep disorder as possibly related to the study drug administration; at the time of last report the adverse event of sleep disorder was persisting. The subject completed the study and was discharged from the unit on Day 15. However, the subject refused to resume his regular medication after discharge. On Day 20, the subject experienced worsening of symptoms of schizophrenia and was readmitted to the hospital. The subject was given oral risperdal 3 mg twice daily. The symptoms improved by Day 25. The Investigator considered the serious adverse event as possibly related to study drug administration. The C_{max} and AUC_{tau} values (219 ng/mL and 2407 ng.h/mL, respectively) calculated on Day 14 in this subject were comparable to the calculated cohort mean C_{max} and AUC_{tau} values (247 ng/mL and 2742 ng.h/mL, respectively) (Attachment 2.3).

- **Subject 071003 (serious adverse event: schizophrenia):** This 36-year-old white man with a history of paranoid schizophrenia since 1990 was randomly assigned to receive dose titrations of JNJ-37822681 from 20 mg to 80 mg once daily, and received JNJ-37822681 for 14 days, with the maximum daily dose of 80 mg achieved on Days 9 to 14. On Day 6, the subject experienced moderate diarrhea, which was treated with 100 mL oral solution of 0.1% potassium permanganate solution and resolved on the same day. The Investigator considered the event of diarrhea as doubtfully related to the study drug administration. On Days 7 and 10, the subject experienced mild tachycardia, which resolved spontaneously on the same day. The Investigator considered both events of tachycardia to be possibly related to study drug administration. On Day 14, the subject experienced mild orthostatic hypotension, which resolved spontaneously on the same day. The Investigator considered the event of orthostatic hypotension as doubtfully related to the study drug administration. The subject completed the study on Day 14. After completion of dosing in the study, the subject was dosed with risperidone 2 mg twice daily for schizophrenia. In a follow-up visit on Day 38, the subject complained of insomnia for the previous 3 days, was observed to have worsening of symptoms of schizophrenia, and was hospitalized. While hospitalized, the subject was treated with standard care for schizophrenia (antipsychotics and benzodiazepines). The subject slowly improved and was discharged after 108 days. The Investigator categorized this as a serious adverse event due to the need for hospitalization during observation after the treatment period, but as doubtfully related to the study drug administration. The C_{max} and AUC_{tau} values calculated on Day 14 in this subject were somewhat lower, ie, 160 ng/mL and 1905 ng.h/mL, respectively, compared to a cohort mean C_{max} of 247 ng/mL and AUC_{tau} of 2742 ng.h/mL (Attachment 2.3).
- **Subject 071004 (serious adverse events, discontinuation due to increased aspartate aminotransferase and increased blood creatine phosphokinase):** This 21-year-old white man with a history of schizophrenia since 2005 was randomly assigned to receive dose titration from 10 mg to 40 mg twice daily over 14 days. The subject ended his previous therapy of sulpiride 200 mg twice daily on Day -2. The subject received JNJ-37822681 for 9 days, and was titrated to a maximum daily dose of 70 mg on Days 8 and 9. On Day 1, the subject experienced mild headache and injection site hematoma, the event of headache resolved spontaneously on the same day and the event of injection site hematoma resolved on Day 6. The Investigator considered the event of headache as doubtfully related and the event of injection site hematoma as not related to the study drug administration. On Day 3, the subject experienced mild dyssomnia, which resolved spontaneously on the next day. The Investigator considered the event of dyssomnia as not related to the study drug administration. On Day 5, the subject experienced mild increased blood lactate dehydrogenase (LDH, 363 U/L, normal range 135 to 225 U/L), moderate increased aspartate aminotransferase (AST, 100 U/L, normal range 0 to 37 U/L) and severe increased blood creatine phosphokinase (CPK, 7,978 U/L, normal range 39 to 308 U/L). The events of increased AST and increased CPK were considered serious adverse events. On Day 7, the subject experienced AST increased to 338 U/L (~9-fold the upper limit of normal [ULN]) and CPK increased to 8,000 (~26-fold ULN). On Day 9, the LDH had returned to the normal range and by Day 14, AST had returned to the normal range. However, CPK was still above the ULN at follow up (426 U/L, Day 23). Treatment with JNJ-37822681 was stopped on Day 9 after the morning dose due to the adverse events of increased AST and CPK. The events of increased AST and CPK were considered by the Investigator as possibly related to the study drug administration. The subject was withdrawn from the study on Day 23. The C_{max} and AUC_{0-12h} values (27.7 ng/mL and 166 ng.h/mL, respectively)

calculated on Day 1 in this subject were slightly higher than the calculated cohort mean C_{max} and AUC_{0-12h} values (21.6 ng/mL and 132 ng.h/mL, respectively) (Attachment 2.3).

- **Subject 071007 (discontinuation due to blood calcium increased):** This 52-year-old white woman with a history of paranoid schizophrenia since 1986 was randomly assigned to receive JNJ-37822681 dose titrations from 10 mg to 40 mg twice daily over 14 days. The subject ended her previous therapy of 1.5 mg haloperidol twice daily on Day –3. At screening on Day -10, the subject had a high blood calcium concentration (3.3 mmol/L, normal range 2.1 to 2.42 mmol/L); the blood calcium concentration was still above ULN on Day 1. The subject received both doses of JNJ-37822681 and the morning dose on Day 2, after which, dosing was stopped at the request of the Sponsor and recommendation was given that the subject be medically evaluated for the cause of her hypercalcemia. The subject was withdrawn from the study on Day 9, due to persisting high blood calcium concentration. The Investigator considered the event of increased blood calcium as not related to the study drug administration. On Day 1, the subject experienced mild increased diastolic blood pressure, which resolved on the same day. The Investigator considered the event of increased diastolic blood pressure as not related to the study drug administration. The C_{max} and AUC_{0-12h} values (20.7 ng/mL and 143 ng.h/mL, respectively) calculated on Day 1 in this subject were comparable to the calculated cohort mean C_{max} and AUC_{0-12h} values (21.6 ng/mL and 132 ng.h/mL, respectively) (Attachment 2.3).
- **Subject 421003 (discontinuation due to suspected Brugada syndrome observed in the ECG):** This 22-year-old white man with a history of paranoid schizophrenia since 2005 was randomly assigned to receive JNJ-37822681 dose titrations from 10 mg to 40 mg twice daily over 14 days. The subject ended his previous therapy of 5 mg olanzepine twice daily on Day –3. The subject was titrated to 60 mg JNJ-37822681 twice daily on Day 7 and received a morning dose of 70 mg JNJ-37822681 on Day 8. Dosing was stopped on Day 8 because of abnormalities observed in his ECG. This subject's ECG had been within normal limits at screening on Day –7, but had been abnormal at predose on Day 1 and for most observations until Day 9. The ECG abnormality was classified as being suspected Brugada syndrome. At follow up on Day 19, the subject's ECG was considered within normal limits. On Day 1, the calculated C_{max} (23.1 ng/mL) in this subject was comparable to the calculated cohort mean C_{max} (21.6 ng/mL) and the AUC_{0-12h} (108 ng.h/mL) was slightly lower compared to the calculated cohort mean AUC_{0-12h} (132 ng.h/mL) (Attachment 2.3).

- As was discussed above, there were 8 subjects who did not titrate up to the full dose of study drug (maximum daily dose of 80 mg JNJ-37822681, administered either as 40 mg twice daily or 80 mg once daily). A summary of adverse events by maximal dose of study medication received is provided in Table 7; although the number of subjects is small, the incidence of specific adverse events did not appear to be significantly different based on the actual exposure to study drug.

Table 7: Incidence of Treatment-Emergent Adverse Events by Maximal Dose Received
(STUDY JNJ37822681-SCH2003: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	20 mg (N=1) n (%)	40 mg (N=1) n (%)	50 mg (N=1) n (%)	60 mg (N=1) n (%)	70 mg (N=4) n (%)	80 mg (N=25) n (%)	Total (N=33) n (%)
Total no. subjects with adverse events	1 (100)	1 (100)	1 (100)	1 (100)	3 (75)	25 (100)	32 (97)
Psychiatric disorders	0	1 (100)	1 (100)	1 (100)	3 (75)	17 (68)	23 (70)
Sleep disorder	0	0	1 (100)	0	0	10 (40)	11 (33)
Insomnia	0	0	0	0	2 (50)	2 (8)	4 (12)
Abnormal dreams	0	0	0	0	0	3 (12)	3 (9)
Anxiety	0	1 (100)	0	0	0	2 (8)	3 (9)
Nightmare	0	0	0	1 (100)	0	2 (8)	3 (9)
Agitation	0	0	0	0	0	2 (8)	2 (6)
Dyssomnia	0	0	0	0	1 (25)	1 (4)	2 (6)
Tension	0	0	0	0	0	2 (8)	2 (6)
Nervous system disorders	0	0	1 (100)	1 (100)	3 (75)	13 (52)	18 (55)
Akathisia	0	0	0	0	1 (25)	6 (24)	7 (21)
Headache	0	0	1 (100)	0	1 (25)	4 (16)	6 (18)
Tremor	0	0	0	0	1 (25)	4 (16)	5 (15)
Gait disturbance	0	0	0	1 (100)	0	1 (4)	2 (6)
Gastrointestinal disorders	0	0	1 (100)	0	0	11 (44)	12 (36)
Diarrhoea	0	0	1 (100)	0	0	4 (16)	5 (15)
Salivary hypersecretion	0	0	0	0	0	3 (12)	3 (9)
Dry mouth	0	0	0	0	0	2 (8)	2 (6)
Nausea	0	0	1 (100)	0	0	1 (4)	2 (6)
Vomiting	0	0	1 (100)	0	0	1 (4)	2 (6)
General disorders and administration site conditions	0	0	0	0	1 (25)	11 (44)	12 (36)
Fatigue	0	0	0	0	0	11 (44)	11 (33)
Musculoskeletal and connective tissue disorders	0	1 (100)	0	1 (100)	0	7 (28)	9 (27)
Musculoskeletal stiffness	0	0	0	1 (100)	0	4 (16)	5 (15)
Muscular weakness	0	0	0	1 (100)	0	2 (8)	3 (9)
Myalgia	0	0	0	1 (100)	0	1 (4)	2 (6)
Investigations	1 (100)	0	0	0	1 (25)	6 (24)	8 (24)
Blood pressure diastolic increased	1 (100)	0	0	0	1 (25)	3 (12)	5 (15)
Blood pressure systolic increased	0	0	0	0	0	2 (8)	2 (6)
Electrocardiogram QT prolonged	0	0	0	0	0	2 (8)	2 (6)
Cardiac disorders	0	0	0	0	1 (25)	6 (24)	7 (21)
Tachycardia	0	0	0	0	1 (25)	6 (24)	7 (21)
Bundle branch block	0	0	0	0	0	2 (8)	2 (6)
Vascular disorders	0	0	0	0	0	7 (28)	7 (21)
Orthostatic hypotension	0	0	0	0	0	5 (20)	5 (15)
Hypotension	0	0	0	0	0	2 (8)	2 (6)
Infections and infestations	0	0	0	0	1 (25)	4 (16)	5 (15)
Nasopharyngitis	0	0	0	0	0	4 (16)	4 (12)
Skin and subcutaneous tissue disorders	0	0	1 (100)	0	0	3 (12)	4 (12)
Hyperhidrosis	0	0	0	0	0	2 (8)	2 (6)

Note: Incidence is based on the number of subjects, not the number of events.
Treatment-Emergent Adverse Events With ≥ 5% of Subjects in Total Treatment Group
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- The majority of adverse events were mild or moderate in intensity (Attachment 3.1). Severe adverse events were reported in 4 subjects: Subject 071003 reported severe schizophrenia 37 days after randomization to 80 mg JNJ-37822681 once daily (see subject narrative above), Subject 071004, randomized to the 40-mg twice-daily group reported severe increased level of blood CPK on Day 3 (actual dose was 15 mg twice daily) and severe increased AST on Day 4 (actual dose was 25 mg twice daily), which were reported as serious adverse events (see subject narrative above), and Subject 071007, randomized to the 40-mg twice-daily group had severe increased level of blood calcium during screening and on Days 2 and 3 (see the subject narrative above). In addition, Subject 461002 experienced severe anxiety due to benzodiazepine abstinence during screening and was not randomized to treatment.
- None of the adverse events were considered by the Investigator to be very likely related to the study drug (Attachment 3.1). The majority of the adverse events reported were considered by the Investigator as probably or possibly related to the study drug. The incidence of probably and possibly related adverse events was similar in both treatment groups.
- A summary of adverse events by preferred term with confidence intervals is provided in Attachment 3.5.
- Seven subjects (4 in the 40-mg twice-daily and 3 in the 80-mg once-daily dosing groups) reported akathisia (Table 6). All the events of akathisia were considered mild or moderate in severity and very likely or probably related to study medication by the Investigator. None of the reports of akathisia were treated with concomitant medication or resulted in a change in dosing of study drug and all resolved.
- In addition to the adverse event information, data on akathisia were compiled using the BARS (see also the discussion on Extra Pyrimidal Symptoms below under Other Safety Findings and Attachment 7.2) and were rated for maximal score over time. In this analysis, 9 subjects in the 40-mg twice-daily JNJ-37822681 group and 7 subjects in the 80-mg once-daily JNJ-37822681 group had questionable, mild, or moderate akathisia (Attachment 3.6). No subjects had marked or severe akathisia, 1 subject in each treatment group had moderate akathisia, and 11 subjects (7 and 4 in the 40-mg twice-daily and 80-mg once-daily JNJ-37822681 dosing groups, respectively, had mild akathisia.
- Three (20%) of subjects in the 80-mg JNJ-37822681 once-daily group reported muscular weakness compared with 0 subjects in the 40-mg JNJ-37822681 twice-daily group (Table 6). The incidence of myalgia was 2 (13%) and 0, respectively. The incidence of musculoskeletal stiffness was 3 (20%) and 2 (11%) respectively.
- Four (22%) subjects randomized to 40-mgJNJ-37822681 twice-daily group reported nasopharyngitis, whereas no subjects in the 80 mg JNJ-37822681 once-daily group reported this event (Table 5).
- Two (13%) subjects (Subject 421005 and 421002) randomized to the 80-mg JNJ-37822681 once-daily group had prolonged QT interval (Table 5), which were mild in severity and resolved spontaneously. QTcF interval remained below 450 msec. The Investigator considered this event as not related (Subject 421005) and probably (Subject 421002) related to the study drug administration, whereas no subjects in the 40-mg JNJ-37822681 twice-daily group had this event.
- Two subjects (Subjects 071006 and 071005) randomized to the 80 mg JNJ-37822681 once-daily group reported mild bundle branch block (SRS 106 msec and 104 msec, respectively) as adverse events, which were considered by the Investigator as doubtfully related to study drug (see also the discussion of ECGs and Attachment 6.4 under Other Safety Findings below).

Other Safety Findings

Laboratory Results

- Means and mean changes over time for hematology, biochemistry, urinalysis laboratory results are provided in Attachments 4.1, 4.2, and 4.3, respectively. Abnormal laboratory values are provided in Attachments 4.4, 4.5, and 4.6, respectively. Several subjects had high CPK levels at baseline. One subject (071004) had increased CPK that was considered a serious adverse event (see the subject narrative above); no other subjects had increased CPK as an adverse event.
- Shifts from baseline for hematology, biochemistry, urinalysis laboratory results are provided in Attachments 4.7, 4.8, and 4.9, respectively. Three subjects had clinically significant abnormalities:
  - Subject 071010 randomized to the 80-mg JNJ 37822681 once-daily group had low hemoglobin, hematocrit, red blood cell count, and absolute reticulocyte level at baseline and throughout the study. The subject was referred for evaluation at the completion of the study.
  - Subject 071007 randomized to the 40 mg JNJ-37822681 twice daily group was noted to be hypercalcemic at screening and had high calcium level of 3.39 mmol/L (normal range: 2.10-2.42 mmol/L) at subsequent visits throughout the study. The hypercalcemia was considered an adverse event and it was recommended by the Sponsor that the subject be discontinued from the study and evaluated for the cause of the hypercalcemia (see also the subject narrative included above under adverse events.)
  - Subject 071004 randomized to the 40 mg JNJ-37822681 twice-daily group had increased CPK (on Days 5 to 14), AST (on Days 5 to 11), and alanine aminotransaminase (ALT) levels (on Days 7 to 11). The increased CPK and AST were considered serious adverse events and led to discontinuation of study medication (see also the subject narrative included above under adverse events.)

Vital Signs

- Shifts from baseline were recorded in vital signs, however, no clinically significant trends were observed (Attachments 5.1 and 5.2).
- Although most subjects reported high diastolic blood pressure (>90 mmHg) or high systolic blood pressure (>140 mmHg) when standing (67% and 58%, respectively) at some time during the study, average blood pressures decreased slightly during treatment compared to baseline. The incidence of blood pressure abnormalities was approximately 10% higher in the 40-mg JNJ-37822681 twice-daily group compared to the 80-mg JNJ-37822681 once-daily group. Increased blood pressure was reported as an adverse event by 5 subjects (Attachment 3.1).

Physical Examinations

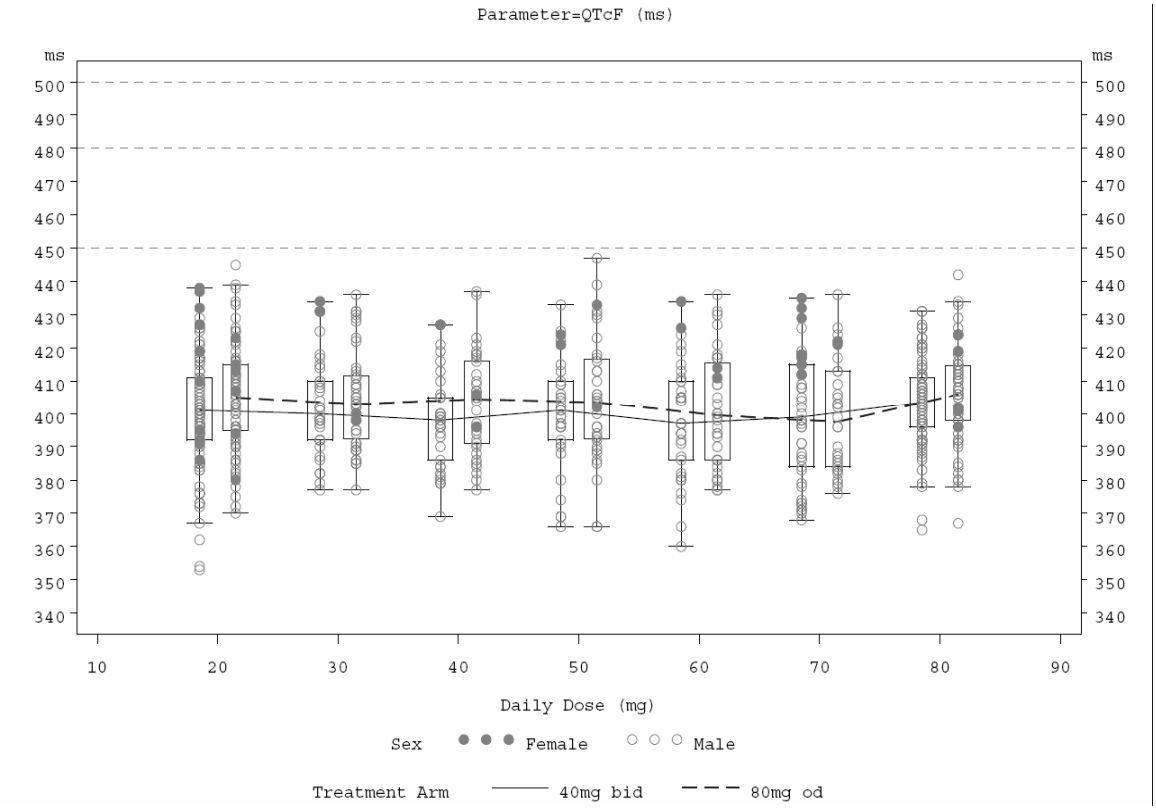
- Six subjects randomized to 40 mg JNJ-37822681 twice daily had physical examination abnormalities during this study, however, none were considered clinically significant by the Investigator (Attachment 3.7).

Electrocardiograms

- Prolonged QTcF intervals (>450 ms) following randomization were not observed in the 40-mg JNJ-37822681 twice-daily or 80-mg once-daily dose groups. One subject (321001) randomized to 80 mg JNJ-37822681 once daily had a screening QTcF value >450 ms (ie, 461 ms).

- None of the subjects had a change from baseline of more than 60 ms in the QTcF intervals. QTcF changes from baseline between 30 and 60 ms were observed in 4 subjects randomized to 40 mg JNJ-37822681 twice daily and 1 subject randomized to 80 mg JNJ-37822681.
- A summary of the QTcF values collected at various timepoints versus daily dose is provided in Figure 3.

Figure 3: Exploration of QTcF Values Versus Daily Dose
(Study 37822681SCH2003)



Extra Pyramidal Symptoms

- In both dose groups the AIMS, BARS, SAS, CGI-SCH, and PANSS results (Attachments 7.1, 7.2, 7.3, 7.4, and 7.5, respectively) were unremarkable and were not clinically significant during the study.

STUDY LIMITATIONS:

- During the study, the main limitation was the small number of subjects identified by the sites associated with PET centers. The decision was made to stop enrollment for the PET scans because so few subjects were recruited by the sites while the recruitment of subjects at all other sites, for the safety and tolerability assessments without PET, was met.
- Of the 33 subjects enrolled in the study, 8 subjects (4 subjects in each treatment group) did not titrate up to the full dose. Three of the 4 subjects randomly assigned to receive a JNJ-37822681 dose titration from 10 mg to 40 mg twice daily over 14 days who did not titrate up to the full dose were discontinued due to adverse events or suspected Brugada syndrome (see Safety Results above), whereas none of the subjects randomly assigned to receive JNJ-37822681 dose titrations of JNJ-37822681 from 20 mg to 80 mg once daily were discontinued from the study due to an adverse event.
- After the study, while not a limitation, the observation of increased CPK as a serious adverse event in 1 subject discussed under Safety Results above, will be added to the Guidance for Investigators in the Investigator's Brochure. While this adverse event appears to be a class effect seen with many other antipsychotics (Meltzer 2000, Terao 1999), it had not been previously described for this compound.

CONCLUSIONS:

- A lower fluctuation was observed with the 40 mg twice-daily dosing regimen compared to the 80 mg once-daily dosing regimen (Day 14, mean C_{max} to $C_{predose}$ ratio of 2:1 versus 4:1).
- The in vivo plasma concentration of JNJ-37822681 at which 50% of striatal D_2-receptor is occupied was estimated to be 29.3 ng/mL with a Hill coefficient estimated to be 0.862 and with E_{max} fixed to 100%.
- Overall, there was a good temporal relationship between the plasma PRL concentrations and the JNJ-37822681 plasma concentrations.
- JNJ-37822681 was safe and well tolerated when administered orally in doses of up to 40 mg twice daily and 80 mg once daily. The incidences of psychiatric and nervous system adverse events were similar in the JNJ-37822681 40-mg twice-daily and 80-mg once-daily treatment groups; more subjects reported gastrointestinal disorders in the 40-mg JNJ-37822681 twice-daily group compared to the 80-mg once-daily group. The most frequently-reported adverse events reported were: sleep disorder, fatigue, akathisia, tachycardia, headache, tremor, diarrhea, musculoskeletal stiffness, increased diastolic blood pressure and orthostatic hypotension; the incidence of fatigue was higher in subjects randomized to the JNJ-37822681 40-mg twice-daily group compared to the 80-mg JNJ-37822681 once-daily group.

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