Name of Finished Product	To be determined
Name of Active Ingredient	JNJ-40411813

Protocol No.: 40411813SCH2001

Title of Study: First-in-Patient Study to Assess the Safety and Tolerability and to Explore the Potential Therapeutic Efficacy of a Novel Glutamate Modulator as Monotherapy and as Add-On Therapy in Patients With Schizophrenia

EudraCT Number: 2010-023369-23

NCT No.: NCT01323205

Clinical Registry No.: CR018340

Coordinating Principal Investigator(s): Dr Bogdan Pacala, MD, PhD - Spitalul de Psihiatrie Sibiu, [redacted] Romania.

Study Center(s): Part A of this study was conducted in 5 clinical centers in 3 countries as follows: Bulgaria (2), Romania (1), and Germany (2); Part B of this study was conducted in 18 clinical centers in 5 countries as follows: Romania (4), Belgium (4), Spain (2), Germany (5), and Austria (3).

Publication (Reference): None.

Study Period: Part A: 21 June 2011 to 04 December 2012; Part B: 13 April 2011 to 29 August 2012. Database lock date: Part A: 10 January 2013; Part B: 25 September 2012.

Phase of Development: Phase 2a

OBJECTIVE:

The primary objectives of this study were to investigate, with JNJ-40411813 as monotherapy or as add-on to antipsychotic medication:

- Safety and tolerability in subjects with schizophrenia;
- Explore potential effect in subjects with schizophrenia;

Secondary objectives:

- To assess pharmacokinetic (PK) parameters of JNJ-40411813 in a patient population using a population PK approach and explore its relationship with efficacy (eg, change in Positive and Negative Syndrome Scale [PANSS] scores) and safety parameters.

METHODS:

This was a multicenter, first-in-patient, safety and tolerability study exploring the potential clinical efficacy of JNJ-40411813 in schizophrenic subjects ([sub]acute and stable subjects). This study included two parts; Part A: an open-label (OL) monotherapy treatment arm, with (sub)acute schizophrenic subjects (JNJ-40411813 monotherapy), and Part B: double-blind (DB), placebo-controlled add-on treatment arm, with stable but symptomatic schizophrenic subjects (JNJ-40411813 add-on therapy to antipsychotic medication). Part A (JNJ-40411813 monotherapy) and Part B (JNJ-40411813 add-on therapy) were to run simultaneously. Participation in Part A excluded enrollment in Part B and vice versa. Approximately 10 investigational sites were to participate in this study and each site was to make every effort to contribute 9 to 12 subjects to the study.

Part A (JNJ-40411813 monotherapy):

- Part A of the study consisted of the following phases: 1) Screening Phase (Day -21 to Day -2), 2) OL Treatment Phase (Week 1 to Week 4), 3) Continuation Phase: Responders Only (Week 5 to Week 12), and 4) Follow-up Phase (approximately 14 days after the last dose of study drug, including withdrawal).
- Fifteen subjects in Part A were to receive JNJ-40411813 in a dose range from 50 to 150 mg twice daily (bid). All subjects were to start receiving 50 mg bid, and the dose was to be gradually increased (minimally over a 4-day period) to 150 mg bid based on the observed tolerability profile, as judged by the investigator.

Part B (JNJ-40411813 add-on therapy):

- Part B of the study consisted of the following phases: 1) Screening Phase (Day -21 to Day -2), 2) DB Treatment Phase (Week 1 to Week 4 [+1 week], 3) OL Phase (Week 5 up to Week 12), and 4) Follow-up Phase (approximately 14 days after the last dose of study drug, including withdrawal).
- Ninety subjects in Part B were to receive either placebo (n=18) or one of 2 dose levels (50 mg bid and maximally 150 mg bid) of JNJ-40411813 (n=36 per dose level) in a DB fashion during the first 4 weeks of treatment, followed by maximally 150 mg bid during the OL Phase for another 6 to 10 weeks. In order to evaluate safety data at the lower dose (50 mg bid) before proceeding with testing the higher dose (150 mg bid), the first 18 subjects that were included in Part B were only to receive either 50 mg bid or placebo during the first 4 (+1) weeks. Upon review of all (unblinded) safety and tolerability data up to Week 4 from the first 18 subjects, and provided an acceptable safety and tolerability profile was obtained, remaining subjects were to be randomized to 50 mg and maximally 150 mg JNJ-40411813 bid or placebo. The DB Treatment Phase could be extended by maximally 1 week in order to prepare for unblinding of the treatment allocation.
- Subjects randomized to active drug for the initial 4 weeks were to receive thereafter JNJ-40411813 as OL treatment for another 6 weeks up to a dose level of maximally 150 mg bid. The subject group starting with placebo for 4 weeks, were to receive JNJ-40411813 as OL treatment for maximally 10 weeks, unless they were regarded as placebo-responders (≥20% improvement in total PANSS score) after 4 weeks compared with baseline. Subjects identified as placebo-responders after 4 weeks were discontinued from the study and referred for treatment based on normal standard of care (eg, pharmacotherapy and/or psychosocial interventions or psychotherapy).

Study Procedures (Part A and Part B)

Examinations

After providing consent, the subjects were to undergo screening procedures which included review of demographics, medical and psychiatric history (especially schizophrenia disease history) and living situation, physical examination (including assessments of body weight, height, and temperature), concomitant medication review, clinical laboratory tests (hematology, biochemistry, urinalysis, serology [HIV antibody, HBsAg, and hepatitis C virus antibody], selected biomarkers [epi{genetic} disease markers], alcohol and drug screen, and serum pregnancy test [for women only]). Blood samples for PK analysis and for prolactin (PRL) were to be collected at Day 1 predose. Vital signs (heart rate [HR], systolic and diastolic blood pressure [BP]) and 12-lead electrocardiogram (ECG) were to be performed at Screening. An orthostasis test (measuring BP in standing position after at least 3 minutes standing) was also to be performed at Screening. A pharmacogenomic blood sample was to be collected on Day 1 from subjects who consented separately to the pharmacogenomic component of the study. Subject participation in pharmacogenomic research was optional. Safety was to be assessed for all subjects throughout the study and was to include the Udvalg for Klinische Undersogelser (UKU) side effect rating scale and a suicidality scale (Columbia Suicide Severity Rating Scale [C-SSRS]). Using a study-developed scale that

included a visual analogue scale and ratings of perceived improvement, subjects were asked to rate their treatment satisfaction and potential effects on appetite.

Assessments

Potential clinical efficacy of JNJ-40411813 was to be evaluated using the PANSS, Clinical Global Impression-Schizophrenia scale (CGI-SCH), and the short version of the Subjective Well-Being under Neuroleptics Scale (SWN) for all the subjects. Optional rating scales were to be only used for subjects in Part B at baseline, if the subject was judged by the investigator as having relevant symptoms in the evaluated dimensions at the clinical interview conducted at Screening. Optional scales included: the Calgary Depression Scale for Schizophrenia (CDSS), the Hamilton Anxiety Rating Scale (HAM-A), and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

All examinations and assessments mentioned above were to be performed at timepoints specified in Time and Events Schedule of the study protocol (Appendix 1).

The original protocol was issued on 30 November 2010 and there were 4 protocol amendments (1 international and 3 country-specific):

Amendment GER-1: (dated 21 Mar 2011) included the following key change:

- Subject who enrolled in Part A of the study were not allowed to receive antipsychotic drug for at least 5 half-lives prior to Day 1, if these 5 half-lives were longer than 5 days.
- The wording in inclusion criteria updated with subject must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- The wording in exclusion criteria updated with administered to jail/forensic psychiatry by governmental or judicial decree.

Amendment INT-1: (dated 10 May 2011) included the following key change:

- The requirement to limit the dose of antipsychotic treatment to ≤400 mg/day chlorpromazine equivalent dose was removed.

Amendment INT-1/GER-2: (dated 19 October 2011) included the following key change:

- To align the protocol to local treatment practice at participating sites in Germany, the stability criterion for subjects in Part B, JNJ-40411813 add-on therapy was reduced from 12 to 6 weeks.

Amendment INT-1/BUL-1: (dated 15 March 2012) included the following key change:

- Participation in the pharmacogenomic component of the study was made optional.

The text in this report is written to reflect all the changes implemented by the protocol amendments.

Number of Subjects (planned and analyzed):

Planned: Part A: Fifteen subjects were planned to be enrolled. Part B: Ninety subjects were planned to be enrolled and randomized to receive either placebo or JNJ-40411813. Of the 90 subjects, the first 18 subjects (12 Active and 6 Placebo) were to be randomly assigned to JNJ-40411813 50 mg bid or placebo for 4 weeks followed by OL Treatment Phase.

Analyzed: Part A: A total of 8 subjects were enrolled and all subjects received OL JNJ-40411813 maximally 150 mg bid; all subjects were withdrawn from the study (3 of 8 subjects were withdrawn due to sponsor termination of Part A of the study, 2 subjects each were withdrawn due to lack of efficacy and withdrawal of consent, and 1 subject was withdrawn due to an adverse event [AE]). Part B: A total of 92

subjects were enrolled and randomly assigned to placebo (N=19), JNJ-40411813 50 mg bid group (N=36) and JNJ-40411813 150 mg bid group (N=37). A total of 58 subjects completed the study.

Diagnosis and Main Criteria for Inclusion:

Men and women subjects between 18 and 65 years of age (inclusive) with a body mass index (BMI) between 18 and 35 kg/m² (inclusive) were to be enrolled in the study.

Subjects who met the Diagnostic and Statistical Manual of Mental Disorders (4th Edition, DSM IV) criteria for schizophrenia (295.10, 295.20, 295.30, 295.60, 295.90), diagnosed at least 1 year prior to screening and who met all other inclusion criteria and did not meet exclusion criteria, were to be enrolled in this study. Subjects were to have either an acute exacerbation with a symptom severity as shown by a total PANSS score of 70 to 120 for Part A or chronic stable symptoms as shown by a total PANSS score of 50 to 90 and must have been receiving antipsychotic therapy for Part B. Subjects were required to be known by the recruiting or the referring psychiatrist for at least 12 months.

Subjects with the following 4 main clinical characteristics were to be included in the study:

Part A:

- (Sub)acute, predominant positive symptoms
  - Subjects with exacerbation of their schizophrenic symptoms who preferred to take a drug with a novel mode-of-action over currently available antipsychotics, either due to negative past experiences or any other reason other than treatment-resistance, were to be included.

Part B:

- Residual positive symptoms (PANSS positive subscore ≥15 and higher than the negative subscore)
  - Subjects having positive symptoms like delusions, hallucinations, formal thought disturbances, depersonalization and/or catatonic symptom like stereotypies for at least 2 months, despite current antipsychotic treatment (except for subjects who were receiving clozapine). They were to have partially responded to previous treatment, but not sufficiently and needed additional antipsychotic therapy.
- Residual negative symptoms (PANSS negative subscore ≥18 and higher than the positive subscore)
  - Subjects suffering from predominant symptoms like affective flattening, diminished volition, decreased expressive gestures and/or social withdrawal and only minor positive symptoms (if at all present). Negative symptoms could be either primary or secondary negative symptoms. Subjects were on antipsychotic medication that was sufficient for suppression of positive symptoms, but which was not effectively treating the subjects' negative symptoms.
- Partially responsive to clozapine
  - Subjects either exhibiting delusions, hallucinations, formal thought disturbances, depersonalization and/or catatonic symptom like stereotypies despite treatment with clozapine for at least several weeks, (preferably for several months), or suffering from affective flattening, diminished volition, decreased expressive gestures and/or social withdrawal. Higher dosages of clozapine had either been tried without success or were contraindicated due to side effects. The psychopathological status was to be present despite treatment with clozapine for 4 months. Subjects were to have had an unsatisfactory response to 2 previous adequate treatments with antipsychotics (at least 6 weeks each).

In Part B (JNJ-40411813 add-on therapy) subject randomization was to be stratified by subject group. At least 10 subjects were to be enrolled in each group and efforts were made to end up with more equally balanced groups.

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

Test Product (for both Part A and Part B):

JNJ-40411813 was supplied as 50 mg hard gelatin capsules containing the active ingredient JNJ-40411813, beads of microcrystalline cellulose, hypromellose, and docusate sodium.

Dose and Mode of Administration, Batch No.:

Part A:

- Subjects were to receive JNJ-40411813 50 mg bid (Batch No.: 10J22/G025, 10J23/G025, and 10J24/G025, and Expiry date: November 2012) on Day 1 and the study drug was to be increased gradually up to a dose level of 150 mg bid, if tolerated. JNJ-40411813 was to be administered orally with a meal.

Part B:

- JNJ-40411813 was to be administered orally with a meal with a dose range from 50 mg (Batch No.: 10J23/G025 and Expiry date: November 2012) to a maximum of 150 mg bid. The initial cohort (n=18) of Part B was to be randomized to treatment with JNJ-40411813 50 mg bid or placebo for 4 weeks in DB Treatment Phase, followed by an OL extension of 6-10 weeks during which the dose was to be escalated up to 150 mg bid in all subjects. Following evaluation of the observed safety and tolerability profile after 4 weeks in these first 18 subjects, subsequently enrolled subjects were randomized to treatment with placebo, 50-, or 150-mg JNJ-40411813 bid for 4 weeks (maximally 5 weeks) in the DB Treatment Phase, followed by an OL extension during which the dose was escalated up to maximally 150 mg bid in all subjects.
- During the DB Phase and subsequent OL extension, it was recommended that titration of JNJ-40411813 to 150 mg bid was to be performed as follows: starting with 50 mg bid on Day 1, then 100 mg bid on Day 2 and Day 3, and finally, 150 mg bid from Day 4 onwards.

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

- The placebo (Batch No.: 10J21/G026, Expiry date: October 2012; Batch No.: 10K22/G026, Expiry date: November 2012) formulation was supplied as hard gelatin capsules containing beads of microcrystalline cellulose identical in appearance to the test product.
- All subjects were to be randomized to receive JNJ-40411813 (50 mg bid or 150 mg bid) or matching placebo orally with a meal for the first 4 weeks of treatment in Part B.

Duration of Treatment:

Part A: The total planned study duration was approximately 119 days: Screening Phase (up to 20 days), OL Treatment Phase (85 days or 12 weeks), and the Follow-up visit (approximately 14 days after the last dose of study drug including withdrawal). The treatment duration of the formal OL Phase was maximally 12 weeks.

Part B: The total planned study duration was approximately 134 (+7) days: Screening Phase (up to 20 days), DB Treatment Phase (29 [+7] days or 4 weeks [+1 week]), OL Treatment Phase (43 to 71 days or 6 to 10 weeks), and the Follow-up visit (approximately 14 days after the last dose of study drug including withdrawal). The DB Treatment Phase could be extended by maximally 1 week in order to prepare for unblinding of the treatment allocation. The total duration of the DB treatment was 4 to 5 weeks. Depending on treatment assignment in the DB Phase, the duration of the OL Phase was 6 weeks (for JNJ-40411813 50 mg bid and 150 mg bid treatment groups) or 10 weeks (for placebo group), so that the maximum exposure to JNJ-40411813 for all treatment groups was 10-11 weeks.

Criteria for Evaluation:

Detailed procedures are provided in the study protocol (Appendix 1).

Efficacy Evaluations:

Following assessments were to be performed to evaluate efficacy:

- Positive and Negative Syndrome Scale: to measure symptom severity of subjects with schizophrenia. This is a 30-item scale with each item rated on a scale of 1 (absent) to 7 (extreme). The PANSS total score is the sum of all 30 PANSS items and ranges from 30 to 210. Higher scores indicate more severe neuropsychiatric symptoms of schizophrenia.
- Clinical Global Impression – Schizophrenia: to rate the severity of a subject's overall clinical condition at a given time, on a 7 point scale from "Not ill" to "Extremely severe." Higher scores denote severe rating. This scale permits a global evaluation of the subject's condition at a given time.
- Subjective Well-being on Neuroleptics Scale: to evaluate the differential effects of antipsychotics and dose on subjective well-being.
- Yale-Brown Obsessive Compulsive Scale: optional scale to be completed at baseline, only if in the investigator's opinion the subject had evidence of relevant obsessive compulsive symptoms during the clinical interview at Screening.
- Hamilton Anxiety Rating Scale: optional scale to be completed at baseline, only if in the investigator's opinion the subject had evidence of relevant symptoms of anxiety during the clinical interview at Screening.
- Calgary Depression Scale for Schizophrenia: optional scale to be completed at baseline, only if in the investigator's opinion the subject had evidence of relevant symptoms of depression during the clinical interview at Screening.
- Self-rating regarding appetite and attitude towards the treatment: This scale was developed within the company and has not been validated.

Pharmacokinetic Evaluations:

Sample Collection and Handling:

- Blood samples for determination of JNJ-40411813 in plasma (3 mL) concentrations, for biomarker analysis (eg, [epi]genetic disease markers and protein profiling) (20 mL), and for the determination of PRL (3.5 mL) were to be collected at the timepoints specified in the Time and Events Schedule of the study protocol (Appendix 1).
- Venous blood samples could be used for the analysis of JNJ-40411813 metabolites and markers related to schizophrenia.

Analytical Procedures:

- Plasma samples were to be analyzed to determine concentrations of JNJ-40411813 using a validated, specific, and sensitive liquid chromatography-tandem mass spectometry (LC-MS/MS) method under the supervision of the sponsor's bioanalytical facility.
- If required, some plasma samples were to be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples could be stored for future analysis of the metabolite profile.

Pharmacokinetic Parameters:

For all subjects, that participated in Part B of the study, the following PK parameters were to be determined based on model predicted plasma concentration-time data at steady state, using nonlinear mixed effect modeling:

C_{max} peak plasma concentration

C_{trough} trough plasma concentration, ie the concentration that was just prior to the beginning of, or at the end, of a dosing interval

C_{avg} average plasma concentration at steady-state

$AUC\tau$ area under the plasma concentration-time curve from 0 to τ hours postdosing at steady state, calculated by trapezoidal summation (time τ was the dosing interval)

Pharmacogenomic Evaluations

- After the subjects consented to pharmacogenomic research, a pharmacogenomic blood sample (10 mL) was to be collected from subjects at the timepoint specified in the Time and Events Schedule of the study protocol (Appendix 1), to allow for the identification of genetic factors that could influence the PK, PD, safety, or tolerability of JNJ-40411813.
- Subjects were to participate in Part 1 (Analysis related to the study) as a requirement for participation in the clinical study and were to be given the option to participate in Part 2 (DNA storage for future research) of the pharmacogenomic component of this study.

Safety Evaluations

- Adverse events were to be reported by the subject for the duration of the study from signing the informed consent form until the follow-up visit.
- Specific clinical laboratory tests (hematology, biochemistry, urinalysis) were to be performed at the timepoints specified in the Time and Events Schedule of the study protocol and are listed in Section 9.6 of the study protocol (Appendix 1).
- The measurements of 12-lead ECGs, vital signs (BP and HR), physical examinations (including height, body weight, and temperature) were to be performed according to the Time and Events Schedule of the study protocol.
- A test for orthostatic hypotension was to be performed at Screening and thereafter as needed during the treatment period.
- The investigator was to make every effort to see that subjects received continuity of care for all those subjects who exited the study – whether they were withdrawn early or had completed the DB Phase.

Other Safety Measures

- Prolactin levels were to be measured at the timepoints specified in the Time and Events Schedule of the study protocol (Appendix 1).
- The Udvalg for Kliniske Undersøgelser: to assess the side effects in subjects treated with psychotropic medications.
- Columbia Suicide Severity Rating Scale: to assess any potential treatment-emergent suicidality (suicidal ideation and or behavior).

Statistical Methods:

The data from all subjects who received at least 1 dose of study drug and had both: baseline and at least 1 postbaseline efficacy measurement were to be included into the efficacy summary tables. The data from all subjects who received at least 1 dose of study drug were to be included in the safety summary tables. All collected information were to be listed. Data from Part A and Part B of the study was analyzed separately.

Sample Size Justification

In this exploratory study, the sample size was not determined based on statistical considerations, but based on clinical judgment. In total, approximately 105 subjects were to participate in the study. Fifteen subjects were to be assigned to Part A (JNJ-40411813 monotherapy) while in Part B (JNJ-40411813 add-on therapy), 90 subjects were to be randomized in the following way: 18 in the placebo group, 36 in the JNJ-40411813 low dose treatment group, and 36 in the JNJ-40411813 high dose treatment group.

Pharmacokinetic Analysis

For Part A and Part B, data were to be listed for all subjects with available plasma concentrations per treatment. Population PK analysis was performed on data from Part B only. Baseline samples excluded for population PK analysis and samples with missing sample and/or dosing records that were excluded for population PK analysis were to be clearly documented in the study report. Graphical exploration of data was to be performed if deemed useful. For each dose in Part B, descriptive statistics, including arithmetic mean, standard deviation (SD), median, minimum, and maximum were to be applied for estimated PK parameters. In addition, available subjects' characteristics (demographics, laboratory variables, and genotypes) could be tested as potential covariates affecting PK parameters.

Plasma samples were analyzed to determine concentrations of JNJ-40411813 using a validated, specific, and sensitive LC-MS/MS method under the supervision of the sponsor's bio-analytical facility.

Nonlinear mixed-effect modeling was applied to explore the PK of JNJ-40411813. Pharmacokinetic data of this study were combined with those of a selection of Phase 1 studies to support a relevant structural model. The developed population PK model was used to predict plasma concentration-time profiles at steady-state and to estimate exposures (C_{0h}, C_{avg}, C_{max} and AUC_{12h}) for each subject that participated in Part B of the study. Details of the population PK analysis were given in a population PK analysis plan and results of the population PK analysis will be presented in a separate population PK report.

Efficacy Analysis

Pharmacodynamic parameters that were to be analyzed were: PANSS Total Score, Symptom-specific questionnaire scores (PANSS Positive Subscale, PANSS Negative Subscale, PANSS Marder Negative Factor), CGI-SCH, and SWN. The following optional scales were to be analyzed when available: CDSS, HAM-A, and Y-BOCS).

Symptom-specific questionnaire scores were to be standardized (using the corresponding baseline value) to obtain Z-scores. Composite Z-score for each subject were to be calculated as mean value of questionnaire-specific Z-scores.

Descriptive statistics (mean, SD, median, and range) for each PD parameter (including Composite Z-score) as well as their changes from baseline were to be calculated. All the PD measurements were to be presented by treatment group and type of subject.

A mixed-effect analysis of variance model that included treatment and time as fixed effects, and subject as a random effect, was to be used to estimate the treatment differences for PANSS total score and Composite Z-score.

Pharmacokinetic/Effect Analyses

The PRL changes from baseline were be explored as a function of the JNJ-40411813 plasma exposure obtained on these days.

When deemed useful based on the safety and efficacy outputs, other PK/effect correlations could be investigated.

Safety Analysis

The safety analysis of all subjects receiving JNJ-40411813 was to include the incidence of AEs (all reported AEs with onset during the treatment phase [ie, treatment-emergent adverse events (TEAEs) and special attention was to be given to those subjects who discontinued treatment due to an AE, or who experienced a severe or a serious adverse event [SAE]), changes in BP, HR, laboratory safety data, 12-lead ECG, physical examination data, UKU (side effect rating scale), C-SSRS (suicidality), and orthostasis test.

Treatment-emergent AEs that were considered related to dizziness were summarized by treatment group and study Phase (DB and OL). The following dizziness-related MedDRA preferred terms were considered: vertigo, ataxia, coordination abnormal, dizziness, disturbance in attention, and dizziness postural.

RESULTS:

The results of this study are provided in 2 parts: Part A and Part B.

STUDY POPULATION:

Part A:

- A total of 8 subjects were enrolled, received OL JNJ-40411813 150 mg bid and were included in the safety analysis set.
- All 8 subjects were withdrawn from the study; 3 of 8 subjects were withdrawn due to sponsor termination of the study, 2 subjects were withdrawn due to lack of efficacy, 2 subjects were withdrawn due to withdrawal of consent, and 1 subject was withdrawn due to an AE.
- All 8 subjects were white, 6 were male and age ranged from 20 to 53 years.
- No protocol deviations were reported.
- Medical history abnormalities and psychiatric history are summarized in Attachments LSUB04 and LSUB05, respectively.

Part B:

- In total, 92 subjects with a DSM-IV diagnosis of schizophrenia entered the DB Phase of the study and were randomly assigned in a 1:2:2 ratio to 1 of the 3 treatment groups (placebo, JNJ-40411813 50 mg bid and JNJ-40411813 150 mg bid) as adjunctive treatment to stable antipsychotic therapy. Of the 92 subjects randomized in the DB Phase, 71 entered the OL Phase and were treated with JNJ-40411813 150 mg bid adjunctive therapy.
- All of the 92 randomized subjects were included in the safety analysis set (defined as receiving at least one dose of study medication) and 82 subjects were included in the Intent-to-Treat (ITT) analysis set (defined as receiving at least one dose of study medication and providing both a baseline and at least 1 post-baseline efficacy assessment).
- Of the 92 randomized subjects, 71 (77%) completed the 4 week DB Phase (Table 1). The most frequent reason for withdrawal was an AE which occurred in 13 subjects (14%).

Table 1: Study Completion/Withdrawal Information During Double Blind Phase (All Randomized)

(Study JNJ40411813 - SCH2001 - Part B: All Randomized Subjects Analysis Set)

Disposition Status Standardized Disposition Term	Placebo (N=19) n (%)	JNJ-40411813 50 mg bid (N=36) n (%)	JNJ-40411813 150 mg bid (N=37) n (%)	Total (N=92) n (%)
Completed Double Blind	17 (89)	29 (81)	25 (68)	71 (77)
Discontinued	2 (11)	7 (19)	12 (32)	21 (23)
Adverse Event	1 (5)	6 (17)	6 (16)	13 (14)
Withdrawal of Consent	0	0	6 (16)	6 (7)
Lack of Efficacy	0	1 (3)	0	1 (1)
Protocol Violation	1 (5)	0	0	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Key: N = total sample size., n = subset of sample size
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- Out of 71 subjects who entered the OL Phase to receive 150 mg JNJ-40411813 bid, 58 (82%) completed the study (Table 2). Withdrawal of consent was the most frequent reason for discontinuation (5 [7%] subjects) in the OL phase of Part B.

Table 2: Study Completion/Withdrawal Information During Open Label Phase

(Study JNJ40411813 - SCH2001 - Part B: All Randomized Subjects Analysis Set)

Disposition Status Standardized Disposition Term	Placebo (N=17) n (%)	JNJ-40411813 50 mg bid (N=29) n (%)	JNJ-40411813 150 mg bid (N=25) n (%)	Total (N=71) n (%)
Completed Study	12 (71)	24 (83)	22 (88)	58 (82)
Discontinued	5 (29)	5 (17)	3 (12)	13 (18)
Withdrawal of Consent	1 (6)	1 (3)	3 (12)	5 (7)
Adverse Event	2 (12)	2 (7)	0	4 (6)
Lost to Follow-up	1 (6)	1 (3)	0	2 (3)
Noncompliance With Study Drug	0	1 (3)	0	1 (1)
Physician Decision	1 (6)	0	0	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: During OL Phase, all subjects received JNJ-40411813 150 mg bid but the data is presented in table by original treatment assignment in DB Phase.
Key: N = total sample size., n = subset of sample size
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A listing of Study Completion/Early Withdrawal Information for all randomized subjects is provided in Attachment LSUB03. The Study Completion/Early Withdrawal Information during DB and OL Phase for ITT population is provided in Attachments DSUB04B and DSUB05B, respectively.

Demographic and Baseline Characteristics

- The demographic and baseline characteristics were consistent and generally comparable between the treatment groups (Table 3). The majority of the subjects were male (67%) and white (98%). The overall mean age of subjects was 42.3 years, ranging from 22 to 65 years, with a mean (SD) baseline body weight of 81.4 (16.10) kg and mean (SD) baseline BMI of 27.0 (4.26) kg/m^2.

- In general, the treatment groups were similar with respect to the baseline characteristics, except for age – subjects in the placebo group were younger (Table 3). Out of 92 randomized subjects, 20 (22%) subjects were partially responsive to clozapine, 47 (51%) had residual negative symptoms and 25 (27%) had residual positive symptoms.
- The demographic and baseline characteristics of the ITT analysis set (Attachment DSUB03A) was similar to the safety analysis set.

Table 3: Demographic and Baseline Characteristics (Safety)

(Study JNJ40411813 - SCH2001 - Part B: Safety Analysis Set)

	Placebo (N=19)	JNJ-40411813 50 mg bid - (N=36)	JNJ-40411813 150 mg bid - (N=37)	Total (N=92)
Age				
N	19	36	37	92
Mean (SD)	38.8 (9.96)	45.8 (8.89)	40.7 (9.39)	42.3 (9.66)
Median	37.0	47.0	41.0	42.0
Range	(23;63)	(28;65)	(22;59)	(22;65)
Baseline Weight (kg)				
N	18	36	37	91
Mean (SD)	83.6 (11.15)	82.1 (18.71)	79.7 (15.61)	81.4 (16.10)
Median	84.5	83.3	78.0	80.9
Range	(68;101)	(48;135)	(52;114)	(48;135)
Baseline Height (cm)				
N	19	36	37	92
Mean (SD)	175.7 (8.57)	174.0 (11.22)	171.9 (9.80)	173.5 (10.15)
Median	178.0	174.0	174.0	174.5
Range	(152;188)	(148;198)	(152;190)	(148;198)
Baseline BMI (kg/M2)				
N	18	36	37	91
Mean (SD)	27.4 (4.40)	26.9 (4.55)	26.9 (3.99)	27.0 (4.26)
Median	26.9	26.2	26.9	26.7
Range	(21;35)	(19;35)	(20;34)	(19;35)
Sex, n (%)				
N	19	36	37	92
Female	4 (21)	14 (39)	12 (32)	30 (33)
Male	15 (79)	22 (61)	25 (68)	62 (67)
Race, n (%)				
N	19	36	37	92
Other	0	1 (3)	0	1 (1)
Unknown	1 (5)	0	0	1 (1)
White	18 (95)	35 (97)	37 (100)	90 (98)
Cohort Description, n (%)				
N	19	36	37	92
Partially Responsive to Clozapine	5 (26)	9 (25)	6 (16)	20 (22)
Residual Negative Symptoms	8 (42)	18 (50)	21 (57)	47 (51)
Residual Positive Symptoms	6 (32)	9 (25)	10 (27)	25 (27)
Ethnicity, n (%)				
N	19	36	37	92
Hispanic or Latino	2 (11)	4 (11)	4 (11)	10 (11)

Not Hispanic or Latino	16 (84)	30 (83)	33 (89)	79 (86)
Not Reported	1 (5)	2 (6)	0	3 (3)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Key: BMI = body mass index, N = total sample size., SD = standard deviation
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- Medical history abnormalities are summarized in Attachment DSUB09. A listing of medical history abnormalities and psychiatric history are provided in Attachments LSUB05 and LSUB06, respectively.

Prior and Concomitant Therapies

- All psychotropic medications received by subjects prior to the DB Treatment Phase are summarized in Attachment DSUB12B. All concomitant medications received during DB and OL Treatment Phase of the study are summarizd in Attachment DSUB14A and Attachment DSUB14B. A listing of subjects with concomitant medications is presented in Attachment LSUB11.

Protocol Deviations

- A total of 28 subjects were reported with major protocol deviations (Attachment DSUB10A). The most frequently reported protocol deviation included “received wrong treatment” or “incorrect dose” (16 [17%] subjects), followed by “entered the study but entry criteria not met” (10 [11%] subjects). On review of specific cases of “received wrong treatment” or “incorrect dose”, 7 subjects had an unacceptable reduced compliance with study medication, 4 subjects had not adhered to the requirement to allow 12 hours between dosing, and 5 subjects had inadvertently temporarily received medication kits allocated to another subject. There was no direct impact in terms of safety or tolerability in any of these cases.
- The protocol deviations were not considered to have impacted the overall results of the study. A listing of Protocol deviations by subject is provided in Attachment LSUB07.
- The protocol deviations for ITT analysis set are summarized in Attachment DSUB10B.

Extent of Exposure

- During the DB Phase, subjects were randomized to receive either JNJ-40411813 (50 mg bid [N=36] or 150 mg bid [N=37]) or placebo (N=19) for 4 to 5 weeks.
- More subjects in the placebo and JNJ-40411813 50 mg bid groups received study medication for at least 29 days than those in the JNJ-40411813 150 mg bid group (placebo: 89%, JNJ-40411813 50 mg bid: 81%, and JNJ-40411813 150 mg bid: 73%) Attachment DSUB11A.
- Mean dose intensity (the ratio of the cumulative actual capsule intake to the total number of capsules prescribed [placebo] or the dose received relative to the expected dose [active]) in the placebo, JNJ-40411813 50 mg bid, and JNJ-40411813 150 mg bid treatment groups was 97.4%, 96.3%, and 88.3%, respectively (Attachment DSUB11A).
- During the OL Phase, all subjects received JNJ-40411813 150 mg bid. Seventy percent of the placebo-DB subjects, 83% of JNJ-40411813 50 mg bid-DB subjects, and 92% of JNJ-40411813 150 mg bid-DB subjects received medication up to and beyond 1 week before study planned end.
- Depending on the randomization assignment in the DB Phase, treatment duration in the OL Phase was 10 weeks (for DB placebo subjects), or 6 weeks (for JNJ-40411813 50 mg bid and JNJ-40411813 150 mg bid DB subjects). The mean dose intensity in the OL Phase was 97.5% (Attachment DSUB11B).

SAFETY RESULTS:

Part A:

All subjects who enrolled and received at least 1 dose of study drug (JNJ-40411813 150 mg bid) were included in the safety analysis set (N=8).

- No deaths were reported in this study.
- One treatment-emergent serious adverse event (TESAE) of psychotic disorder was reported in Subject [redacted] which was considered as not related to study drug (Attachment LAE03). The detailed narrative for this subject is provided in Attachment NARR_SAE_SCH2001.
- One subject (Subject [redacted] was withdrawn from the study due to a TEAE of psychotic disorder (reported term: worsening of psychotic symptoms) (Attachment LAE05).
- The most common TEAEs reported in more than 1 subject were psychotic disorder (3), asthenia (2), insomnia (2), and palpitations (2).
- All TEAEs were mild or moderate in intensity and only 1 TEAE was reported as severe (Attachment LAE04).
- The majority of TEAEs were reported as probably or not related to JNJ-40411813 150 mg bid (Attachment LAE04).
- There were no clinically significant laboratory findings (Attachment LLAB03).
- No clinically significant ECG abnormalities were reported (Attachments LECG01A and LECG01B).
- There were no clinically significant changes in the vital signs (systolic and diastolic BP [standing and supine], pulse rate, body weight, temperature, and BMI) (Attachments LVS01, LVS02, and LVS03).

Part B:

Data Sets Analyzed

Summaries of AEs and other safety data are based on 92 subjects in the DB Phase, and 71 subjects in the OL Phase, who had at least 1 dose of the study drug, and were included in the safety analysis set of Part B. In the DB Phase, subjects were randomly assigned to placebo (N=19) or the active treatment group, ie, JNJ-40411813 (total N=73; 36 subjects in 50 mg bid group and 37 subjects in 150 mg bid group). In the OL Phase, all subjects received JNJ-40411813 150 mg bid. Data are shown for all subjects together and by original randomization assignment during the DB Phase.

Summary of All Adverse Events

Overall summary of safety data for both the DB and OL Treatment Phases are discussed below (Attachments DAE08A and DAE08B):

- There were no deaths reported in Part B of the study.
- Three (3%) subjects were reported with TESAEs during the DB Phase and 6 (8%) subjects were reported with TESAEs in the OL Phase. The detailed narratives are provided in Attachment NARR_SAE_SCH2001.
- Fourteen (15%) subjects were withdrawn from the study due to TEAEs during the DB Phase, and 3 (4%) subjects were withdrawn during the OL Phase.
- In the DB Phase, 13 (18%) subjects in the JNJ-40411813 treatment groups discontinued due to TEAEs (7 [19%] in JNJ-40411813 50 mg bid group and 6 [16%] in JNJ-40411813 150 mg bid

group), showing a higher rate of study discontinuation for the active versus the placebo group (1 [5%]).

- During the OL Phase, study discontinuation due to TEAEs was comparable in subjects originally randomized to placebo (1 [6%]) and JNJ-40411813 (2 [4%]).

Double-Blind (DB) Phase

- Overall, 48 (52%) of 92 subjects experienced at least 1 TEAE. Both JNJ-40411813 treatment groups showed a higher incidence of TEAEs (41 [56%] subjects, comprised of 22 [61%] subjects in the JNJ-40411813 50 mg bid group, and 19 [51%] subjects in the JNJ-40411813 150 mg bid group), compared with the placebo group (7 [37%]). A summary of TEAEs for the DB Treatment Phase is given in Table 4.
- Three subjects reported TESAEs in the JNJ-40411813 150 mg bid group (Attachment NARR_SAE_SCH2001):
  - Subject [redacted] had schizophrenia catatonic type; Subject [redacted] had ECG abnormal; both these events were considered doubtfully related to study drug by the investigator
  - Subject [redacted] had psychotic disorder which was considered not related to study drug by the investigator.
- No TESAEs were reported in the placebo group. A listing of subjects with SAEs is provided in Attachment LAE03.
- The most common TEAEs during the DB Phase (>10% of subjects in any treatment group) that occurred more frequently in the JNJ-40411813 treatment groups than in the placebo group were: nausea, headache (including tension headache), dizziness, and vertigo.
- Headache (including tension headache) was most common in the JNJ-40411813 50 mg bid group, occurring in 6 (17%) subjects. In the placebo and JNJ-40411813 150 mg bid groups, headache occurred in 2 (11%) and 3 (8%) subjects, respectively.
- Dizziness and vertigo were experienced most frequently in subjects randomized to the JNJ-40411813 150 mg bid group, occurring in 6 (16%) and 4 (11%) subjects, respectively. Only 1 (5%) subject was reported with dizziness in the placebo treatment group and 1 (3%) subject in the JNJ-40411813 50 mg bid treatment group. No vertigo was observed in the placebo treatment group, while in the JNJ-40411813 50 mg bid group, vertigo occurred in 2 (6%) subjects.
- Nausea was observed in 4 (11%) and 6 (16%) subjects in the JNJ-40411813 50 mg bid and JNJ-40411813 150 mg bid treatment groups, respectively. No nausea occurred in the placebo group (Table 4).
- Constipation, fatigue, and psychotic disorder were each reported by 4 (5%) of 73 subjects in both JNJ-40411813 treatment groups. All other TEAEs were reported by ≤3 subjects.
- Most of the TEAEs in the JNJ-40411813 treatment groups were considered as possibly, probably or very likely related to the study agent by the investigator (Attachment DAE05A).
- A total of 12 TEAEs in the JNJ-40411813 treatment groups were reported as severe in intensity by the investigator. The majority (11) of these severe TEAEs were reported in the JNJ-40411813 150 mg bid group as follows: nausea (2), psychotic disorders (2), vertigo (2), disturbance in attention (1), tension headache (1), diarrhea (1), schizophrenia catatonic type (1), and fatigue (1); only 1 severe TEAE (ie, enteritis) was reported in the JNJ-40411813 50 mg bid group (Attachment LAE01).
- Thirteen (18%) subjects withdrew from the study due to TEAEs in the JNJ-40411813 treatment groups (7 [19%] subjects in the JNJ-40411813 50 mg bid group, and 6 [16%] subjects in the

JNJ-40411813 150 mg bid group), and only 1 (5%) subject withdrew in the placebo group. The most common TEAEs leading to study withdrawal in the subjects dosed with JNJ-40411813 were psychotic disorder (3 [4%] subjects) and vertigo (2 [3%] subjects). All other TEAEs resulting in discontinuation were only reported by 1 subject (Attachments LAE05 and DAE06A).

- Fifteen (16%) subjects experienced dizziness-related AEs (dizziness [8 {9%}], dizziness postural [1 {1%}], vertigo [6 {7%}], and coordination abnormal [1 {1%}]), out of which only 1 (5%) subject was from the placebo group and 14 (19%) subjects were from the JNJ-40411813 treatment groups (3 [8%] subjects in JNJ-40411813 50 mg bid and 11 [30%] subjects in JNJ-40411813 150 mg bid) (Attachment DAE09A).

Table 4: **Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term During the Double-Blind Phase**

(Study JNJ-40411813-SCH2001-Part B: Safety Analysis Set)

	Placebo	JNJ-40411813 50mg bid	JNJ-40411813 150mg bid	Active Total	Total
Body System Or Organ Class	(N=19)	(N=36)	(N=37)	(N=73)	(N=92)
Dictionary-Derived Term	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events in Double-Blind Phase	7 (37)	22 (61)	19 (51)	41 (56)	48 (52)
Nervous System Disorders	2 (11)	10 (28)	11 (30)	21 (29)	23 (25)
Headache	0	6 (17)	2 (5)	8 (11)	8 (9)
Dizziness	1 (5)	1 (3)	6 (16)	7 (10)	8 (9)
Sedation	0	2 (6)	1 (3)	3 (4)	3 (3)
Tremor	0	0	2 (5)	2 (3)	2 (2)
Akathisia	0	1 (3)	0	1 (1)	1 (1)
Disturbance in Attention	0	0	1 (3)	1 (1)	1 (1)
Dizziness Postural	0	0	1 (3)	1 (1)	1 (1)
Dyskinesia	0	1 (3)	0	1 (1)	1 (1)
Somnolence	0	0	1 (3)	1 (1)	1 (1)
Tension Headache	2 (11)	0	1 (3)	1 (1)	3 (3)
Coordination Abnormal	1 (5)	0	0	0	1 (1)
Gastrointestinal Disorders	2 (11)	7 (19)	10 (27)	17 (23)	19 (21)
Nausea	0	4 (11)	6 (16)	10 (14)	10 (11)
Constipation	0	2 (6)	2 (5)	4 (5)	4 (4)
Diarrhoea	1 (5)	1 (3)	2 (5)	3 (4)	4 (4)
Dry Mouth	0	0	1 (3)	1 (1)	1 (1)
Enteritis	0	1 (3)	0	1 (1)	1 (1)
Hiatus Hernia	0	0	1 (3)	1 (1)	1 (1)
Salivary Hypersecretion	0	1 (3)	0	1 (1)	1 (1)
Vomiting	0	0	1 (3)	1 (1)	1 (1)
Abdominal Discomfort	1 (5)	0	0	0	1 (1)
Psychiatric Disorders	2 (11)	4 (11)	7 (19)	11 (15)	13 (14)
Psychotic Disorder	0	2 (6)	2 (5)	4 (5)	4 (4)
Agitation	1 (5)	1 (3)	1 (3)	2 (3)	3 (3)
Abnormal Dreams	0	0	1 (3)	1 (1)	1 (1)
Anxiety	0	0	1 (3)	1 (1)	1 (1)
Catatonia	0	0	1 (3)	1 (1)	1 (1)
Confusional State	0	0	1 (3)	1 (1)	1 (1)
Depression	1 (5)	1 (3)	0	1 (1)	2 (2)
Fear	0	0	1 (3)	1 (1)	1 (1)
Hallucination, Olfactory	0	0	1 (3)	1 (1)	1 (1)
Ideas of Reference	0	0	1 (3)	1 (1)	1 (1)

Restlessness	1 (5)	1 (3)	0	1 (1)	2 (2)
Schizophrenia, Catatonic Type	0	0	1 (3)	1 (1)	1 (1)
Terminal Insomnia	0	0	1 (3)	1 (1)	1 (1)
General Disorders and Administration Site Conditions	1 (5)	3 (8)	5 (14)	8 (11)	9 (10)
Fatigue	0	1 (3)	3 (8)	4 (5)	4 (4)
Asthenia	1 (5)	0	1 (3)	1 (1)	2 (2)
Chest Discomfort	0	1 (3)	0	1 (1)	1 (1)
Chest Pain	0	1 (3)	0	1 (1)	1 (1)
Feeling Abnormal	0	0	1 (3)	1 (1)	1 (1)
Malaise	0	0	1 (3)	1 (1)	1 (1)
Infections and Infestations	1 (5)	4 (11)	3 (8)	7 (10)	8 (9)
Nasopharyngitis	1 (5)	2 (6)	1 (3)	3 (4)	4 (4)
Gastrointestinal Infection	0	1 (3)	0	1 (1)	1 (1)
Rhinitis	0	0	1 (3)	1 (1)	1 (1)
Tracheobronchitis	0	1 (3)	0	1 (1)	1 (1)
Urinary Tract Infection	0	1 (3)	0	1 (1)	1 (1)
Viral Upper Respiratory Tract Infection	0	0	1 (3)	1 (1)	1 (1)
Ear and Labyrinth Disorders	0	2 (6)	4 (11)	6 (8)	6 (7)
Vertigo	0	2 (6)	4 (11)	6 (8)	6 (7)
Investigations	1 (5)	2 (6)	2 (5)	4 (5)	5 (5)
Hepatic Enzyme Increased	0	1 (3)	1 (3)	2 (3)	2 (2)
Blood Pressure Increased	0	1 (3)	0	1 (1)	1 (1)
Electrocardiogram Abnormal	0	0	1 (3)	1 (1)	1 (1)
Alanine Aminotransferase Increased	1 (5)	0	0	0	1 (1)
Metabolism and Nutrition Disorders	1 (5)	1 (3)	3 (8)	4 (5)	5 (5)
Decreased Appetite	1 (5)	1 (3)	2 (5)	3 (4)	4 (4)
Hyperglycaemia	0	0	1 (3)	1 (1)	1 (1)
Eye Disorders	0	0	2 (5)	2 (3)	2 (2)
Blepharospasm	0	0	1 (3)	1 (1)	1 (1)
Vision Blurred	0	0	1 (3)	1 (1)	1 (1)
Reproductive System and Breast Disorders	1 (5)	1 (3)	1 (3)	2 (3)	3 (3)
Dysmenorrhoea	0	1 (3)	0	1 (1)	1 (1)
Ejaculation Disorder	0	0	1 (3)	1 (1)	1 (1)
Menorrhagia	1 (5)	0	0	0	1 (1)
Musculoskeletal and Connective Tissue Disorders	1 (5)	1 (3)	0	1 (1)	2 (2)
Pain in Extremity	0	1 (3)	0	1 (1)	1 (1)
Neck Pain	1 (5)	0	0	0	1 (1)
Renal and Urinary Disorders	0	0	1 (3)	1 (1)	1 (1)
Polyuria	0	0	1 (3)	1 (1)	1 (1)
Respiratory, Thoracic and Mediastinal Disorders	1 (5)	0	1 (3)	1 (1)	2 (2)
Upper Respiratory Tract Inflammation	0	0	1 (3)	1 (1)	1 (1)
Oropharyngeal Pain	1 (5)	0	0	0	1 (1)
Injury, Poisoning and Procedural	1 (5)	0	0	0	1 (1)

Complications					
Traumatic Haematoma	1 (5)	0	0	0	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Open Label (OL) Phase

- During the OL Phase, 37 (52%) of 71 subjects in total (who all received JNJ-40411813 150 mg bid) experienced at least 1 TEAE. A summary of TEAEs for the OL Treatment Phase is given in Table 5.
- A total of 6 (8%) subjects reported TESAEs during the OL Phase. Subjects [redacted] and [redacted] had psychotic disorder; Subject [redacted] had anxiety and psychotic disorder; Subject [redacted] had hyponatraemia, and all were considered as not related to JNJ-40411813 by the investigator. Subject [redacted] had augmentation of negative symptoms of schizophrenia and Subject [redacted] had high level of anxiety, both of which were considered doubtfully related to JNJ-40411813 by the investigator. The detailed narratives for these subjects are provided in Attachment NARR_SAE_SCH2001.
- The most frequently reported TEAEs by SOC were gastrointestinal disorders (15 [21%]), followed by psychiatric disorders and nervous system disorders (both 12 [17%]) (Attachment DAE10B).
- The most common TEAE during the OL Phase, during which all subjects received JNJ-40411813 150 mg bid, was nausea, reported in 8 subjects (11%).
- Subjects initially randomized to placebo or JNJ-40411813 50 mg bid in the DB Phase, experienced higher incidences of nausea (24% and 10%, respectively) and dizziness (12% and 10%, respectively), than those initially randomized to JNJ-40411813 150 mg bid during the DB Phase (4% nausea and 4% dizziness). Vomiting, headache, and vertigo occurred in 18% of subjects initially randomized to placebo. Incidences of these AEs in subjects initially randomized to JNJ-40411813 50 mg bid and 150 mg bid were: vomiting (3% and 4%, respectively), headache (0% and 4%, respectively) and vertigo (0% and 4%, respectively) (Table 5).
- A total of 5 TEAEs were reported as severe in intensity by the investigator during the OL Phase. The reported severe TEAEs were as follows: abdominal pain, convulsion, hyponatraemia, vomiting, and psychotic disorder (Attachments LAE01).
- The TEAEs were considered as either not related, doubtful, possibly, or probably related to the study drug in the JNJ-40411813 treatment groups (Attachment DAE05B). None of the TEAEs were assessed as very likely related to the study agent.
- Three (4%) subjects were permanently withdrawn from the study due to TEAEs during the OL Phase. Subject [redacted] had convulsion, face injury, and hyponatraemia; Subject [redacted] had dizziness and nausea; and Subject [redacted] had asthenia and fatigue, all of these TEAEs resulted in permanent discontinuation of study agent (Attachments LAE05 and DAE06B).
- Overall, 11 (15%) of 71 subjects who entered the OL Phase experienced dizziness-related AEs (dizziness [6 {8%}], dizziness postural [1 {1%}], and vertigo [4 {6%}]). Dizziness related AEs were noted in 6 (35%) subjects who were initially randomized to placebo during the DB Phase. In comparison, 3 (10%) subjects and 2 (8%) subjects who were randomized to JNJ-40411813 50 mg bid and JNJ-40411813 150 mg bid, respectively, during the DB Phase experienced dizziness-related AEs in the OL Phase (Attachment DAE09B).

Table 5: Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term During the Open-Label Phase

(Study JNJ40411813-SCH2001-Part B: Safety Analysis Set)

	Placebo	JNJ-40411813 50 mg bid	JNJ-40411813 150 mg bid	Active Total	Total
Body System Or Organ Class	(N=17)	(N=29)	(N=25)	(N=54)	(N=71)
Dictionary-Derived Term	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events in Open-Label Phase	14 (82)	13 (45)	10 (40)	23 (43)	37 (52)
Gastrointestinal Disorders	7 (41)	3 (10)	5 (20)	8 (15)	15 (21)
Nausea	4 (24)	3 (10)	1 (4)	4 (7)	8 (11)
Diarrhoea	0	1 (3)	2 (8)	3 (6)	3 (4)
Vomiting	3 (18)	1 (3)	1 (4)	2 (4)	5 (7)
Gastrooesophageal Reflux Disease	0	0	1 (4)	1 (2)	1 (1)
Haemorrhoidal Haemorrhage	0	0	1 (4)	1 (2)	1 (1)
Abdominal Pain	1 (6)	0	0	0	1 (1)
Dry Mouth	1 (6)	0	0	0	1 (1)
Oesophageal Pain	1 (6)	0	0	0	1 (1)
Psychiatric Disorders	4 (24)	4 (14)	4 (16)	8 (15)	12 (17)
Psychotic Disorder	0	3 (10)	0	3 (6)	3 (4)
Anxiety	1 (6)	1 (3)	1 (4)	2 (4)	3 (4)
Restlessness	1 (6)	1 (3)	1 (4)	2 (4)	3 (4)
Insomnia	1 (6)	0	1 (4)	1 (2)	2 (3)
Nervousness	0	1 (3)	0	1 (2)	1 (1)
Schizophrenia	1 (6)	0	1 (4)	1 (2)	2 (3)
Social Fear	0	1 (3)	0	1 (2)	1 (1)
Inappropriate Affect	1 (6)	0	0	0	1 (1)
Infections and Infestations	1 (6)	4 (14)	2 (8)	6 (11)	7 (10)
Nasopharyngitis	1 (6)	3 (10)	2 (8)	5 (9)	6 (8)
Gastroenteritis Viral	0	1 (3)	0	1 (2)	1 (1)
Influenza	0	1 (3)	0	1 (2)	1 (1)
Nervous System Disorders	7 (41)	3 (10)	2 (8)	5 (9)	12 (17)
Dizziness	2 (12)	3 (10)	1 (4)	4 (7)	6 (8)
Headache	3 (18)	0	1 (4)	1 (2)	4 (6)
Convulsion	1 (6)	0	0	0	1 (1)
Dizziness Postural	1 (6)	0	0	0	1 (1)
Parosmia	1 (6)	0	0	0	1 (1)
Somnolence	1 (6)	0	0	0	1 (1)
Tension Headache	1 (6)	0	0	0	1 (1)
Eye Disorders	0	1 (3)	2 (8)	3 (6)	3 (4)
Blindness Transient	0	0	1 (4)	1 (2)	1 (1)
Eye Irritation	0	1 (3)	0	1 (2)	1 (1)
Vision Blurred	0	0	1 (4)	1 (2)	1 (1)
Cardiac Disorders	0	1 (3)	1 (4)	2 (4)	2 (3)
Tachycardia	0	0	1 (4)	1 (2)	1 (1)
Ventricular Extrasystoles	0	1 (3)	0	1 (2)	1 (1)
General Disorders and Administration Site Conditions	3 (18)	2 (7)	0	2 (4)	5 (7)
Asthenia	0	1 (3)	0	1 (2)	1 (1)
Fatigue	1 (6)	1 (3)	0	1 (2)	2 (3)

Pain	0	1 (3)	0	1 (2)	1 (1)
Chest Pain	1 (6)	0	0	0	1 (1)
Pyrexia	1 (6)	0	0	0	1 (1)
Skin and Subcutaneous Tissue Disorders	0	1 (3)	1 (4)	2 (4)	2 (3)
Hyperhidrosis	0	1 (3)	0	1 (2)	1 (1)
Seborrhoeic Dermatitis	0	0	1 (4)	1 (2)	1 (1)
Ear and Labyrinth Disorders	3 (18)	0	1 (4)	1 (2)	4 (6)
Vertigo	3 (18)	0	1 (4)	1 (2)	4 (6)
Injury, Poisoning and Procedural Complications	1 (6)	0	1 (4)	1 (2)	2 (3)
Thermal Burn	0	0	1 (4)	1 (2)	1 (1)
Face Injury	1 (6)	0	0	0	1 (1)
Investigations	0	0	1 (4)	1 (2)	1 (1)
White Blood Cell Count Increased	0	0	1 (4)	1 (2)	1 (1)
Musculoskeletal and Connective Tissue Disorders	0	1 (3)	0	1 (2)	1 (1)
Myalgia	0	1 (3)	0	1 (2)	1 (1)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (3)	0	1 (2)	1 (1)
Dyspnoea	0	1 (3)	0	1 (2)	1 (1)
Metabolism and Nutrition Disorders	1 (6)	0	0	0	1 (1)
Hyponatraemia	1 (6)	0	0	0	1 (1)
Renal and Urinary Disorders	1 (6)	0	0	0	1 (1)
Enuresis	1 (6)	0	0	0	1 (1)
Reproductive System and Breast Disorders	1 (6)	0	0	0	1 (1)
Galactorrhoea	1 (6)	0	0	0	1 (1)
Vascular Disorders	1 (6)	0	0	0	1 (1)
Hypertension	1 (6)	0	0	0	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Reported dictionary version: MedDRA 15.1
Key: N = total number of subjects; n = size of subsample
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Clinical Laboratory Tests

- During the DB Phase, overall, 8 subjects (9%) had a markedly abnormal treatment-emergent laboratory result. The most frequently observed markedly abnormal result was leukocytosis, in 4 subjects (4%) and the finding was evenly distributed over the treatment groups (Attachment DLAB03A).
- During the OL Phase, overall 8 subjects (11%) had markedly abnormal laboratory values, with the most frequent being leukocytosis (4 subjects [6%] overall) (Attachment DLAB03B).

Vital Signs, ECG, Examination

- Although incidental increases in pulse rate from ≥15 to ≥100 beats/min were observed, there were no differences between treatment groups. In general, there were no clinically meaningful changes in the vital signs (systolic and diastolic BP [standing and supine], pulse rate, body weight, temperature and BMI). Body weight remained stable during both study phases in all treatment groups. (Attachments DVS01, DVS02A, DVS02B and DVS03).
- During the DB and OL Phases, some treatment-emergent abnormal HR findings were observed on ECG (Attachments DECG04A and DECG04B), but there did not appear to be any consistent or clinically significant changes.
- Elevation of QTcB and QTcF >450 ms were observed in both the DB and OL Phase, mostly in the JNJ-40411813 150 mg bid treatment group (Attachments DECG03A, DECG03B, DECG06A, DECG06B, DECG07A, DECG07B). During the OL Phase, 8 subjects (12.1%) had a QTcF increase of >30-60 msecs compared to OL baseline (Attachments LECG05, LECG06, DECG02A, DECG02B). However, there were no cases where both QTcB and QTcF were >500 ms in either study phase and none of the subjects had an increase of more than 60 msecs.
- Isolated increases in QTcB values that occurred mostly during the DB treatment period corresponded to increased HR relative to baseline. Combined increases in QTcB and QTcF that mostly occurred during the OL Phase were generally related to the relatively lower baseline value at the end of the DB treatment phase and within the subjects' normal variation prior to beginning study treatment.
- QTc elevations in 2 subjects (Subject [redacted] and Subject [redacted]) were not explained by elevated HR or normal variation described above. An isolated (OL Day 57) increase in QTcB and QTcF >30 msec to 440 and 410 msec, respectively, was observed in Subject [redacted] (M, 27 years) who received various concomitant medications (100 mg trazodone bid, 45 mg mirtazepine once daily [qd], 200 mg quetiapine bid, 9 mg paliperidone qd, 10 mg clorazepate bid) during the study. Another isolated (OL Day 43) increase in QTcB and QTcF > 30 msec to 460 and 458 msec, respectively, was observed in Subject [redacted] (F, 51 years) who was concomitantly treated with 15 mg aripiprazole qd. Of note, this subject ([redacted] was diagnosed with ventricular extrasystoles (reported term: ventricular arrhythmia extrasystolica) on OL Day 30 and was started on sotalol. The relationship to study drug for this AE was reported as possible. (Attachment LECG01A).
- Only one ECG abnormality was considered by the investigator to be a TESAE (Subject ID: [redacted] in the JNJ-40411813 150 mg bid treatment group), who reported with ECG abnormal with non significant T wave abnormality. Of note, the subject had a pre-existing history of coronary artery disease and the investigator reported the finding as of doubtful relationship to the study drug. The detailed narrative for this subject is provided in Attachment NARR_SAE_SCH2001.

Other Safety Measures:

Part A:

- There were no clinically meaningful changes from baseline observed in PRL values in JNJ-40411813 150 mg bid treatment group (Attachment LLAB02).
- There was no consistent pattern or trend of change observed in the UKU Side Effect Rating Scale (Attachment LOTH01).
- There were no clinically significant suicide-related events in any of the subjects while receiving JNJ-40411813 150 mg bid (Attachment LOTH03).

Part B:

- There were no clinically meaningful changes from baseline observed in PRL values in any of the treatment groups (Attachment DLAB02).

- There was no consistent pattern or trend of change observed in the UKU Side Effect Rating Scale during either the DB or OL Phases. Listing of UKU Side Effect Rating Scale during DB and OL Phase are provided in Attachments LOTH01A and LOTH01B, respectively.
- Overall, there was no evidence of treatment-emergent suicidal-related AEs observed across any of the treatment groups (placebo, JNJ-40411813 50 mg bid, and JNJ-40411813 150 mg bid). A listing of C-SSRS scores is provided in Attachment LOTH03.

PHARMACOKINETIC RESULTS

For Part A (JNJ-40411813 monotherapy), all data (ie, baseline samples and post-baseline samples) are listed in Listings PK1. For Part B (JNJ-40411813 add-on therapy) data are listed for all subjects with available plasma concentrations in Listings PK2. The data from Part B of this study were included in a population PK analysis, which will be reported in a separate population PK report. Baseline samples excluded for population PK analysis and samples with missing sample and/or dosing records that were excluded for population PK analysis are listed in Listings PK3 and PK4, respectively.

Empirical Bayesian estimates for C_{0h}, C_{avg}, C_{max} and AUC_{12h} were obtained for each subject that participated in Part B of the study. The estimated exposures of JNJ-40411813 by subject, visit day and dose for subjects that received JNJ-40411813 or placebo during the DB Phase and JNJ-40411813 during the OL Phase, are listed in Listings PK5 and Listings PK6, respectively. Summary statistics of the estimated exposures of JNJ-40411813 per visit day and dose is provided in Listings PK7 for subjects that received JNJ-40411813 during the DB Phase and JNJ-40411813 during the OL Phase, and in Listings PK8 for subjects that received placebo during the DB Phase and JNJ-40411813 during the OL Phase. Results of the population PK analysis will be presented in a separate report.

EFFICACY RESULTS:

Changes from planned analyses:

- Not all the analyses specified in the statistical analysis plan were conducted due to a small sample size in patient subtype groups, which influenced model convergence.
- The Composite Z-Score on DB Day 29 (described below) was analyzed using a mixed model repeated measures (MMRM) with treatment, time, and time-by-treatment interaction as factors. An unstructured variance-covariance matrix was employed.

Part A:

Efficacy data for all randomized subjects were listed. Due to a small sample size, no summary tables were created.

PANSS Total Score

- There was no consistent pattern of change in PANSS Total scores from baseline to study endpoint. The sample size (N=8) was too small to draw any conclusions regarding clinical efficacy.
- There was no consistent pattern or trend of change observed in Marder Negative Factor Score (Attachment LEFF01).

Clinical Global Impression – Schizophrenia − Severity of Illness

- There was no consistent pattern or trend of change observed in CGI-SCH Severity scores (Attachment LEFF02).

Subjective Well-Being on Neuroleptics Scale

- There was no consistent pattern or trend of change observed in the SWN scale (Attachment LEFF03).

Self-Rating Regarding Appetite and Attitude

- There was no consistent pattern or trend of change observed in self rating regarding appetite and attitude towards treatment while receiving JNJ-40411813 150 mg bid (Attachment LOTH02).

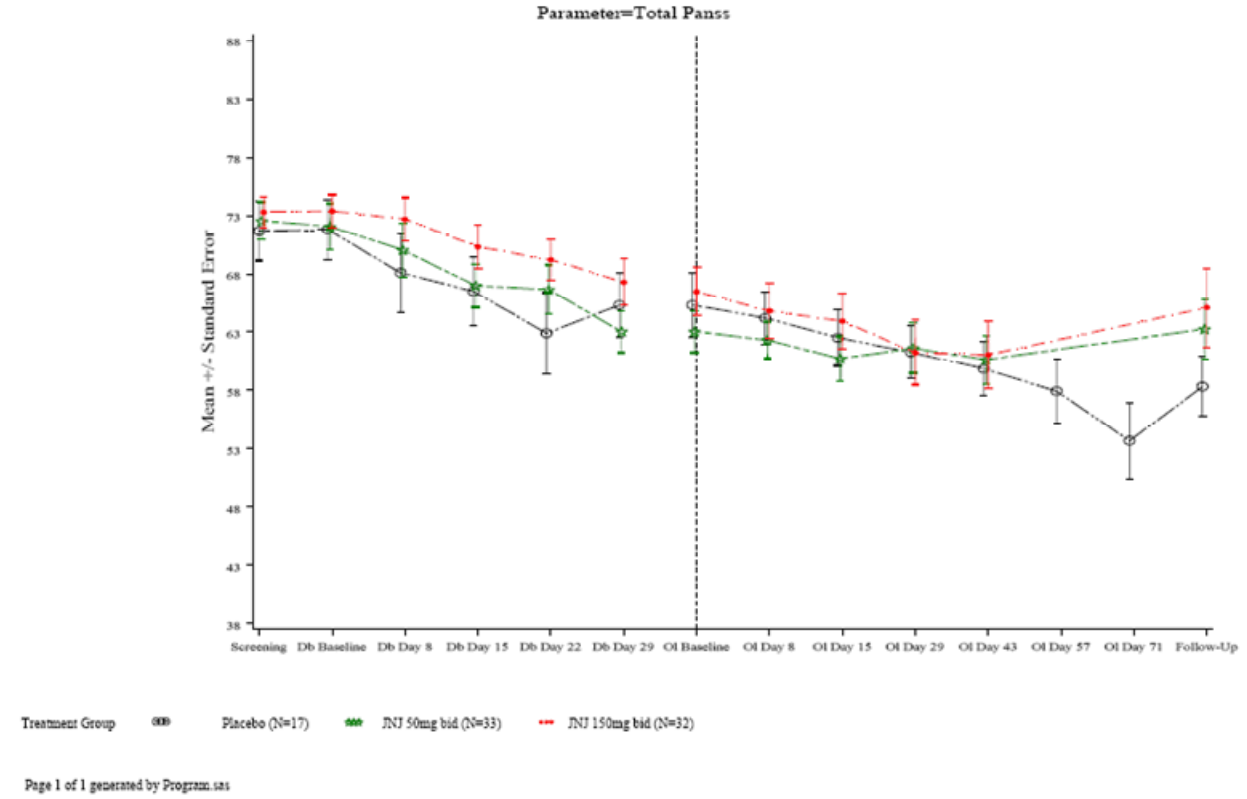
Part B:

- All efficacy summaries are based on the ITT analysis set which comprises all randomized subjects who received at least 1 dose of study medication and provided both a baseline and at least 1 post-baseline efficacy assessment (N=82).
- A sensitivity analysis was done using a Per Protocol (PP) analysis set which consisted of the same subjects who were in the ITT population but who did not have a major protocol deviation during the study (N=51).
- Efficacy results in relation to treatment allocation (JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo bid) are presented separately for all subjects together and where meaningful, for particular subgroups (residual positive symptoms, residual negative symptoms, and partially responsive to clozapine).
- Efficacy data is summarized at the end of the DB Treatment Phase (Day 29).

PANSS Total Score

- Baseline PANSS total score values were comparable across treatment groups when all subjects were considered regardless of clinical phenotype (eg, residual positive, residual negative and partially responsive to clozapine): 71.8 in the placebo group (N=17), 72.8 in the JNJ-40411813 50 mg bid group (N=29), and 73.4 in the JNJ-40411813 150 mg bid group (N=27) (Attachment DEFF01A).
- Change from baseline on DB Day 29 in the PANSS total score was analyzed using a MMRM on the observed case data, with treatment, time, and time-by-treatment interaction as factors, and baseline PANSS total score as a covariate. An unstructured variance-covariance matrix was employed.
- The least-squares adjusted mean (LS Mean [standard error {SE}]) change from baseline to DB Day 29 in PANSS total score was -6.5 (2.2) in the placebo group (N=17), -9.1 (1.6) in the JNJ-40411813 50 mg bid group (N=29), and -4.6 (1.7) in the JNJ-40411813 150 mg bid group (N=27) (Attachment DEFF02).
- There was no statistically significant (p-value: 0.353) difference between the JNJ-40411813 50 mg bid group and the placebo group. The difference between JNJ-40411813 150 mg bid and placebo was also not statistically significant (p-value: 0.492) (Attachment DEFF02).
- Least-squares adjusted mean change over time during the DB Phase, together with SE estimates from the MMRM model, are presented in Attachment FEFF02. Actual scores together with SE estimates are shown in Figure 1, below:

Figure 1: PANSS Total Score by Treatment -Actual Values (Mean+/–SE)
(Study JNJ40411813 - SCH2001 - Part B: Intent-to-Treat Analysis Set)



- As a sensitivity analysis, an MMRM analysis for the change in PANSS Total score was performed on the PP analysis set. The results corroborated the findings from the model employed on the ITT analysis set. Neither of the active treatments was statistically significantly different from placebo (Attachment DEFF04).

Subjects with Partial Response to Clozapine

- Only 4, 3, and 5 subjects that were partially responsive to clozapine had Day 29 data following JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo, respectively.
- The placebo response in PANSS total score during the DB Phase was considerable. Mean change from baseline (SD) in PANSS total score following JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo was -9.3 (8.2), -1.3 (3.5), and -16.2 (6.6), respectively (Attachment DEFF03).

Subjects with Residual Negative Symptoms

- Seventeen, 15 and 8 subjects with residual negative symptoms had Day 29 data following JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo, respectively.
- Subjects who received JNJ-40411813 50 mg improved more in the PANSS total score than subjects receiving placebo or JNJ-40411813 150 mg bid. Mean change from baseline (SD) in PANSS total score following JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo was -10.8 (9.9), -6.1 (6.8), and -5.8 (4.2), respectively (Attachment DEFF03).

Subjects with Residual Positive Symptoms

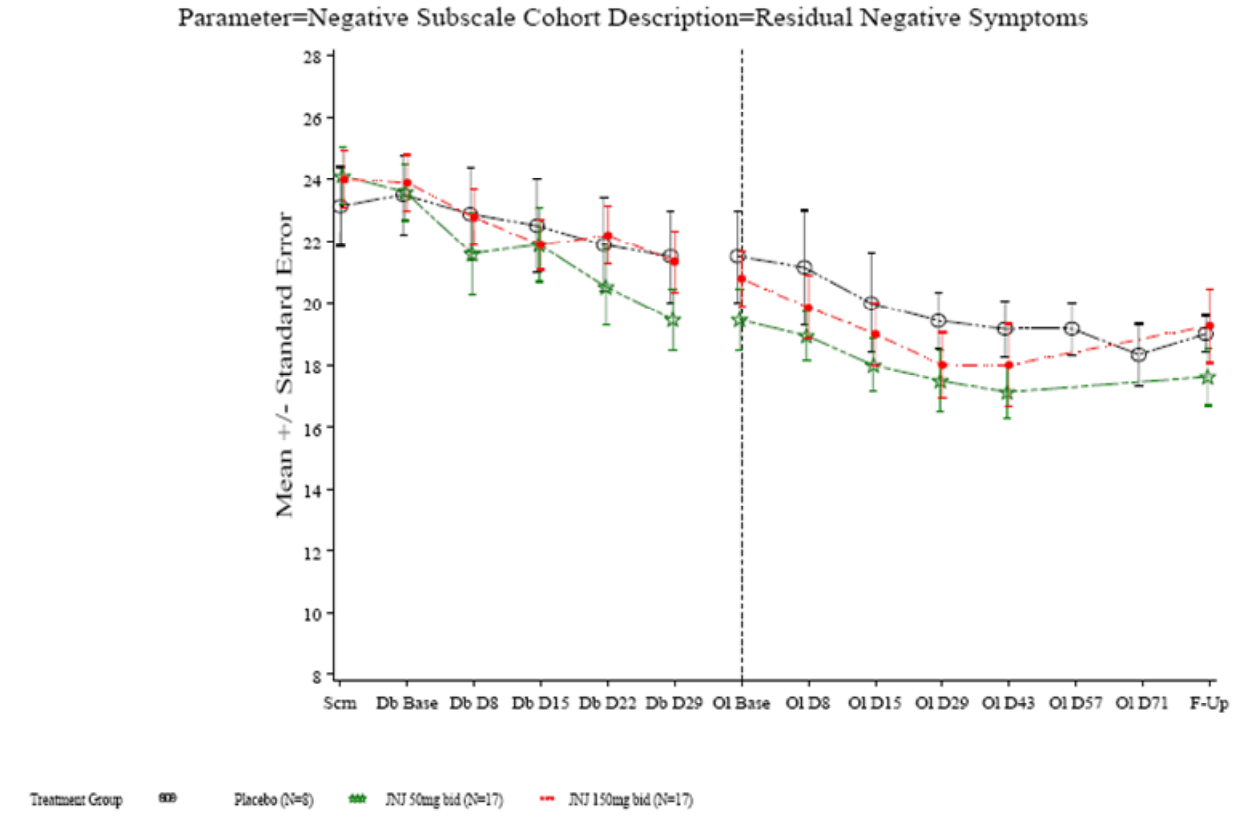
- Eight, 9 and 4 subjects with residual positive symptoms had Day 29 data following JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo, respectively.
- Subjects appeared to have improved more on Day 29 when receiving active treatment than placebo. Mean change from baseline (SD) in PANSS total score following JNJ-40411813 50 mg bid, JNJ-40411813 150 mg bid, and placebo was -8.0 (8.2), -7.8 (7.0), and 4.3 (11.5), respectively. (Attachment DEFF03).

Actual mean (SE) PANSS total score values over time, by patient type and treatment for partially responsive to clozapine, residual negative symptoms, and residual positive symptoms are presented in Attachment FEFF01B.

PANSS Negative Subscale and Negative Symptom Marder Factor Score for Subjects with Residual Negative Symptoms

- Baseline PANSS Negative Subscale Marder Factor scores were comparable across treatment groups. Change from baseline in PANSS Negative Subscale on DB Day 29 of -2.0 was observed in the placebo group (N=8), -4.1 in the JNJ-40411813 50 mg bid group (N=17), and -3.1 in the JNJ-40411813 150 mg bid group (N=15) (Attachment DEFF05B). PANSS Negative Subscale score mean values together with SE over time are presented in Figure 2:

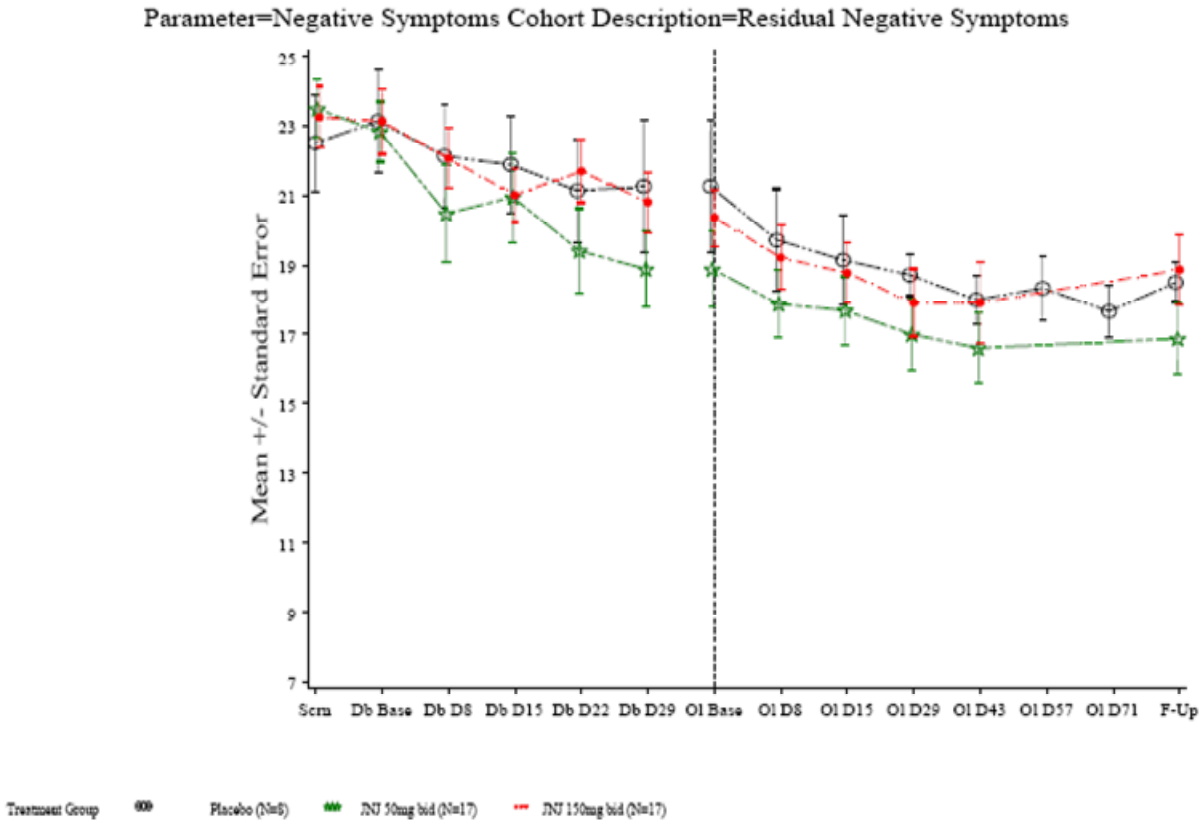
Figure 2: PANSS Negative Subscale by Patient Type and Treatment -Actual Values (Mean+/–SE)
(Study JNJ40411813 - SCH2001 - Part B: Intent-to-Treat Analysis Set)



- Baseline PANSS Negative Symptom Marder Factor scores were also comparable across treatment groups. Change from baseline in PANSS Negative Symptoms Marder score on DB Day 29 of -1.9 was observed in the placebo group (N=8), -3.9 in the JNJ-40411813 50 mg bid group (N=17), and -3.3 in the JNJ-40411813 150 mg bid group (N=15) (Attachment DEFF05B). Negative Symptoms Marder score mean values together with SE over time are presented in Figure 3.

Figure 3: PANSS Negative Symptoms Marder Score by Patient Type and Treatment -Actual Values (Mean+/–SE)

(Study JNJ40411813 - SCH2001 - Part B: Intent-to-Treat Analysis Set)



Clinical Global Impression – Schizophrenia − Severity of Illness

Overall Severity

- The median change from baseline to DB Day 29 for the CGI-SCH Overall Severity score was 0.0 (range: -2 to 0) for all of the 3 treatment groups, with a negative change indicating improvement. Mean change from baseline to DB Day 29 was -0.53 for the placebo group (N=17), and -0.48 and -0.33 for the JNJ-40411813 50 mg bid (N=29) and 150 mg bid (N=27) treatment groups, respectively. When analyzed by subtype, no relevant treatment differences were observed in the CGI-SCH overall scores for residual positive symptoms, depressive symptoms, and cognitive symptoms (Attachment DEFF10A).

Subjects with Residual Negative Symptoms

- The median change from baseline to DB Day 29 for the CGI-SCH Overall Severity score for subjects with residual negative symptoms was 0.0 (range -1 to 0) for the placebo group and JNJ-40411813 150 mg bid group. Subjects treated with JNJ-40411813 50 mg bid, had median change from baseline of -1 (range -2 to 0) and a greater mean change from baseline than subjects

treated with placebo and JNJ-40411813 150 mg bid. Mean changes from baseline on DB Day 29 were -0.65 for JNJ-40411813 50 mg bid (N=17) and -0.38 and -0.33 for placebo (N=8) and JNJ-40411813 150 mg bid (N=15), respectively (Attachment DEFF10B).

- The frequency distribution over time in the CGI−SCH degree of change, by treatment and subject type during DB Phase, is presented in Attachment DEFF12A. The bar-chart for the frequency of the CGI-SCH for Overall Severity scores at DB baseline and end of DB Phase is shown in Attachment FEFF05A.

Subjective Well-Being on Neuroleptics (SWN) Scale

- All subjects receiving placebo or JNJ-40411813 50- and 150 mg bid had an increase in the mean SWN total score from baseline to DB Day 29, with a greater mean score indicating improvement. The mean change from baseline (SD) to DB Day 29 for the SWN total score was 5.5 (11.6) for placebo (N=17), 4.5 (9.2) for JNJ-40411813 50 mg bid (N=29), and 5.6 (9.0) for JNJ-40411813 150 mg bid (N=26) treatment groups (Attachment DEFF13A).
- The mean change from baseline to DB Day 29 for the SWN total score for subjects with residual negative symptoms was 6.8 (5.8) for placebo group (N=8), 4.0 (9.5) for JNJ-40411813 50 mg bid (N=17), and 4.9 (10.3) for JNJ-40411813 150 mg bid (N=15) treatment groups. The placebo response in SWN total score for subjects with residual negative symptoms during the DB Phase was considerable.
- The mean change from baseline to DB Day 29 for the SWN total score for subjects with residual positive symptoms was -5.0 (11.7) for placebo group (N=4), 4.3 (9.5) for JNJ-40411813 50 mg bid (N=8), and 4.3 (6.8) for JNJ-40411813 150 mg bid (N=8) treatment groups. The active treatment groups (JNJ-40411813 50 mg bid and JNJ-40411813 150 mg bid) showed higher response in SWN total score than placebo group.
- Baseline SWN total score for subjects with partially responsive to clozapine were comparable across treatment groups. The mean change from baseline to DB Day 29 for the SWN total score for subjects with partially responsive to clozapine was 12.0 (14.6) for placebo group (N=5), 7.3 (9.7) for the JNJ-40411813 50 mg bid (N=4), and 12.7 (4.9) for the JNJ-40411813 150 mg bid (N=3) treatment groups (Attachment DEFF13B).

Optional Scales: Hamilton Anxiety (HAM-A) Rating Scale, CDSS, and Y-BOCS

- The rating of depressive, anxious and obsessive-compulsive symptoms was optional, as per protocol. The optional scales were first to be completed at baseline, if in the investigator's opinion the subject had evidence of relevant symptoms (anxiety, depression or obsessive-compulsive) during the clinical assessment at Screening. Unless relevant symptoms were also present at Screening, the optional scales were not to be used to rate treatment emergent symptoms during the study. Overall, the use of the additional scales was not consistent across sites and the dataset too small to allow for meaningful interpretation.

Symptom−Specific Composite Z−Scores

- To obtain symptom-specific questionnaire Z-scores, the PANSS Positive and Negative Subscales, as well as HAM-A and CDSS questionnaire scores were standardized. Standardization was done using mean and SD from the questionnaire-respective baseline scores across all subjects. For each subject, a symptom-specific composite Z-score was calculated as mean of all available symptom-specific Z-scores relevant for the patient type (Table 6).

Table 6: Construction of Composite Z-Scores by Patient Type

Patient type	Symptom-specific Z-Scores by patient type
Residual negative symptoms	Z-score (PANSS Negative Subscale), Z-Score (CDSS) and Z-Score (HAM-A)
Residual positive symptoms	Z-score (PANSS Positive Subscale), Z-Score (CDSS) and Z-Score (HAM-A)
Partially responsive to clozapine	Z-Score (CDSS) and Z-Score (HAM-A)

- On DB Day 29 there was an improvement in Mean Composite Z-Score over baseline of 0.26 SD in the placebo group, 0.30 SD in the JNJ-40411813 50 mg bid group, and only 0.06 SD in the JNJ-40411813 150 mg bid group (Attachment DEFF18).
- The Composite Z-Score on DB Day 29 was analyzed using an MMRM with treatment, time and time-by-treatment interaction as factors. An unstructured variance-covariance matrix was employed. The least-squares adjusted mean change from baseline to DB Day 29 in Composite Z-score was -0.26 in the placebo group, -0.33 in the JNJ-40411813 50 mg bid group, and -0.02 in the JNJ-40411813 150 mg bid group, where decrease from baseline represents improvement. The test for difference between the JNJ-40411813 50 mg bid group and the placebo group did not reach statistical significance (p-value: 0.805). The difference between JNJ-40411813 150 mg bid and placebo was also not statistically significant (p-value: 0.382) (Attachment DEFF18).

Self-Rating Regarding Appetite and Attitude

- Across treatments, there were no clinically relevant mean changes observed in self ratings regarding appetite and attitude towards treatment (Attachments DOTH01A and DOTH01B).

PHARMACOGENOMIC RESULTS:

- The pharmacogenomic results will be reported separately.

STUDY LIMITATIONS:

- This study was not powered to demonstrate significant differences in efficacy between treatment groups.
- Due to small sample size, no meaningful conclusions can be drawn about potential drug effects.

CONCLUSION(S):

- No deaths were reported in this study. A total of 10 subjects reported TESAEs (in both Part A and Part B) and all were considered doubtfully, or not related to study drug.
- During the DB Phase, a higher rate of study discontinuation was observed due to TEAEs in the JNJ-40411813 treatment groups compared with placebo.
- Subjects treated with antipsychotics who experienced residual negative symptoms were identified as the subgroup of subjects who may potentially benefit from add-on treatment with JNJ-40411813, with 50 mg bid being the dose with the best benefit/risk profile.
- No notable changes were observed in serum PRL levels as compared to baseline values in both parts of the study.
- There was no evidence that JNJ-40411813 had a clinically relevant adverse effect on any clinical laboratory, vital sign, or cardiovascular safety parameter measured during the study.

- The 50 mg bid dose of JNJ-40411813 was demonstrated to be safe and well-tolerated, with the best benefit-to-risk profile of the 2 doses studied. Tolerability may be further improved by initiating therapy using a dose titration scheme.

REFERENCES

None.

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STUDY TITLE: First-in-Patient Study to Assess the Safety and Tolerability and to Explore the Potential Therapeutic Efficacy of a Novel Glutamate Modulator as Monotherapy and as Add-On Therapy in Patients With Schizophrenia.

STUDY AUTHOR(S): [redacted] DPhil; [redacted] PhD; [redacted] MD; [redacted] MSc; [redacted] MD; [redacted] PhD; [redacted] MD

SPONSOR'S RESPONSIBLE MEDICAL OFFICER

NAME: Justine Kent, MD

TITLE: [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: [redacted] M.D.

DATE: 18 APR 2013

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