**Janssen Research & Development ***

**Clinical Protocol**

# A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Efficacy, Safety, and Tolerability of JNJ-42165279 in Subjects with Social Anxiety Disorder.

**Protocol 42165279SAX2001; Phase 2a**

**Amendment INT-3**

**JNJ-42165279**

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312)

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**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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## PROTOCOL AMENDMENTS

| Protocol Version | Issue Date |
|---|---|
| Original Protocol | 16 Jan 2015 |
| Amendment INT-1 | 14 Apr 2015 |
| Amendment INT-2 | 28 Sept 2016 |
| Amendment INT-3 | 25 August 2017 |

Amendments below are listed beginning with the most recent amendment.

**Amendment INT-3 (25 August 2017)**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

- The overall reason for the amendment:
- To update the information on toxicology
- Based on a regulatory decision, to allow women of childbearing potential to participate in this study under conditions of pregnancy testing and the use of high quality contraception.
- Adaptation of the number of subjects participating in the study. This will be changed from 122 to 137 to replace 15 subjects who had to stop early when the study was put on hold.
- Change in allowed medication and control of drug intake.
- Add the optional use of a diary or electronic device to document the intake of study medication.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Based on a regulatory decision, to allow women of childbearing potential to participate in this study under conditions of pregnancy testing and the use of high quality contraception | |
| Synopsis | Safety Evaluations<br>Added:<br>In all women, serum and urine pregnancy test will be performed at Screening and Follow-up and urine pregnancy test at study visits 2 and 9. In women of childbearing potential (WOCBP), urine pregnancy test will be performed at all other timepoints. If the urine pregnancy test is positive, a serum β-hcg test will be performed. |
| Time & Events schedule | Added: pregnancy test for WOCBP at each visit.<br>Added: Footnote u: Urine pregnancy test in WOCBP only. If the urine pregnancy test is positive, a serum β-hcg test will be performed. Investigators may perform additional pregnancy testing at their discretion as clinically needed. |
| Section 1.1 | Text on spermatogenesis and reproductive toxicology added to reflect recent non-clinical study results. |
| Section 3.2. Population | Added:<br>Given the observation in the rat reproductive toxicology studies (see Section 1.1), WOCBP will only be included if they agree to ongoing use of a highly effective method of birth control (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly). All WOCBP will have a pregnancy test at screening, each study visit and at follow-up. WOCBP constitute a large part of the target population in clinical practice. Safety and efficacy data in this population are important for future clinical studies. |
| Section 4.1 Inclusion criteria | Inclusion criteria 6 and 7 will be replaced by:<br>6.1. Before randomization, a woman must be either:<br>• Not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 12 months, or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/L); permanently sterilized (e.g., tubal |

occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy

- Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly). This may include:
    - Established and ongoing use of oral hormonal methods of contraception in combination with barrier methods.
    - Established and ongoing use of patch, injected or implanted hormonal methods of contraception.
    - Placement of an IUD or IUS.

    Accepted barrier methods as indicated above include:
    - condom with spermicidal foam/gel/film/cream/suppository
    - occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

    Note that a barrier method on its own is not sufficient.

    - Male partner sterilization (the vasectomized partner should be the sole partner for that subject).
    - True abstinence (when this is in line with the preferred and usual lifestyle of the subject).

    Women must agree to continue using these methods of contraception throughout the study and for at least 3 months after receiving the last dose of study medication.

    Note: If a woman of childbearing potential who is not heterosexually active becomes active after the start of the study, she must begin a highly effective method of birth control, as described above.
- All women must have a negative pregnancy test at screening and a negative urine pregnancy test on study day 1.
- All women must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after receiving the last dose of study drug.

7.1. Men who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control e.g., either condom or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners should also use an additional method of birth control (which may include a hormonal method, an intrauterine device [IUD] or an intrauterine system [IUS]) for at least the same duration.

Section 9.1.2, 9.1.3 and 9.1.4

Added: urine pregnancy test at visits 3 to 8 for WOCBP and serum and urine pregnancy test at screening and follow-up for all women (to be consistent with the Time and Events schedule).

Section 9.2.6

Changed text on pregnancy test:

- In all women: serum β-HCG and urine pregnancy test will be performed at Screening and Follow-up and urine pregnancy test at study visits 2 and 9.
- In WOCBP: urine pregnancy test will be performed at all other timepoints.

- If the urine pregnancy test is positive, a serum β-HCG test will be performed.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Adaptation of the number of subjects participating in the study. This will be changed from 122 to 137 to replace 15 subjects who had to stop early when the study was put on hold | |
| Synopsis and Sections 3.1, 4.0 and 11.2 | Changed 122 subjects participating in this study into 137 subjects. |
| Synopsis and Section 11.2 | Added sentence: To replace 15 subjects who prematurely stopped the study when the study was put on hold, the total number of subjects entering the study will be increased from 122 to 137. |
| **Rationale:**<br>• Better clarify that administration of study medication at the site needs to be witnessed by study site personnel.<br>• Remove ramelteon from the list of allowed nonbenzodiazepine sleep aids. Ramelteon is a melatonine agonist. | |
| Section 6 | Added in last paragraph: ..which will be witnessed by designated study-site personnel at the study sites. |
| Section 9.1.3 | Replaced:<br><br>Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.<br><br>by:<br><br>Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites. |
| Section 8 | Replaced:<br><br>Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon, eszopiclone, and ramelteon) are allowed on a PRN (as needed) basis during the study.<br><br>by<br><br>Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon and eszopiclone) are allowed on a PRN (as needed) basis during the study.<br><br>Added to list of "Other prohibited medication":<br><br>- melatonine **and ramelteon**. |
| **Rationale:** Add the optional use of a diary or electronic device to document the intake of study medication. | |
| Synopsis and Section 6, T&E schedule | Added: The sponsor may optionally develop tools to improve and/or document compliance to intake of study medication when locally feasible. This may include a diary or an electronic registration tool. |
| **Rationale:**<br>Numbering of exclusion criterion 6 not correct after amendment 2. | |
| Section 4.2 | Replaced:<br><br>6. Subject has clinically significant abnormal findings on physical examination, neurological examination or clinically significant abnormal vital signs indicative of untreated illness (such as infection or hypertension). |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| | by:<br><br>6. Criterion modified by Amendment 2.<br>6.1. Subject has clinically significant abnormal findings on physical examination, neurological examination or clinically significant abnormal vital signs indicative of untreated illness (such as infection or hypertension). |

**Amendment INT-2** (28 Sep 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** The overall reason for the amendment is to add neurological examinations to confirm the safety of participation in the trial and treatment with JNJ-42165279.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Synopsis | Safety Evaluations<br>Physical examination, **neurological examination**, vital signs, body temperature …will be performed during the study to monitor subject safety. |
| Time & Events schedule. | - Neurological examination added at screening, during the treatment phase and at the end of treatment visit (or early withdrawal visit)<br>- Footnote "t" added : A neurological examination will also be completed in case of adverse event of interest. |
| 4.2 Exclusion criteria | Exclusion criteria 6 has been updated as follows:<br>Subject has clinically significant abnormal findings on physical examination, **neurological examination** or clinically significant abnormal vital signs indicative of untreated illness (such as infection or hypertension). |
| 9.1.2 Screening Phase | Neurological examination added |
| 9.1.3 Double-Blind Treatment Phase | Neurological examination added at Week 4, Week 8 and Week 12 visits |
| 9.2.5 Physical **and Neurological** Examinations | Title updated and text added:<br>The neurological examination can be adapted as necessary but should include mental status (orientation and memory); oculomotor motion and vision for cranial nerve testing; limb strength and abnormal movements for motor function; and tests of cerebellar function: gait, finger-to-nose, heel-to-shin, and rapid alternating movements. Tests of sensation (e.g., pain, vibration) should be included only if indicated by clinical history/symptoms.<br><br>The neurological examination will be done at screening, during the treatment phase and at the end of treatment visit (or early withdrawal visit) for all subjects. In addition neurological examinations will be completed when event driven. These events of interest include diplopia, vision impairment, gait disturbance and severe headache. |
| 11.4 Safety Analysis | Sub title updated as follows: Physical **and Neurological** Examinations |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 12.2 Special Reporting Situations | Text added:<br>For this study safety events of interest include diplopia, vision impairment, gait disturbance and severe headache. These events will trigger a neurological examination and a narrative of the event. |

**Amendment INT-1 (14 Apr 2015)**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** The overall reason for the amendment is to address the comments raised by the Health Authorities of the United States of America and of Canada on safety issues.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Request to exclude women of child bearing potential until the risk for teratogenic effects is better understood. | |
| 4.1. Inclusion Criteria; | Inclusion criteria 6 has been updated as follows:<br>**For this study only women who are not able to bear children will be enrolled**. Before entry, female subjects must meet the following criteria depending on reproductive stage:<br>• Postmenopausal, defined as<br>– >45 years of age with amenorrhea for at least 18 months, or<br>– >45 years of age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/mL, or<br>• Menstrual<br>– Surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy)<br>~~– If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, and for at least 3 months after intake of the last dose of study drug, or~~<br>~~– Not heterosexually active~~<br>~~Note: Women who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study. Women must agree to continue using the same method(s) of contraception throughout the study and for at least 3 months after receiving the last dose of study drug.~~<br>Inclusion criteria 7 of the original protocol has been deleted:<br>~~If a woman of childbearing potential, she must have a negative serum and urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening; and a negative urine pregnancy test on Day 1 (before receiving study drug).~~ |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Synopsis – Time & Events schedule. | - Frequency of pregnancy tests updated (tests deleted on Weeks 1, 2, 4 and 8).<br>- Footnote "k" updated : Performed for all women ~~of childbearing potential~~. |
| 4.3 Prohibitions and Restrictions | First paragraph of the original protocol related to women of child bearing potential has been deleted |
| **Rationale:** Request that the interval between adverse event assessments and routine clinical labs should not exceed 2 weeks. | |
| Synopsis – Time & Events schedule. | Safety visits added at Week 6 (Day 42) and Week 10 (Day 70) |
| 9.1.3. Double-Blind Treatment Phase | Safety visits added at Week 6 (Day 42) and Week 10 (Day 70):<br>The following assessments will be performed as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.<br>• Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)<br>• C-SSRS<br>• Record adverse events and concomitant medication |
| **Rationale:** | Clarification of stopping rules. |
| 3.3.1. Individual Stopping crieria | QTcF replaced by QTcB in the third bullet.<br>• Because of limited information on the effects of JNJ-42165279 on the human liver function a subject will be discontinued from the study if either of the following occur:<br>– Aspartate transaminase (AST) and/or alanine transaminase (ALT) >3 x Upper Limit of Normal (ULN) (confirmed by repeat),<br>– ~~AST and/or ALT >3 x ULN AND~~ Total bilirubin >~~1.5~~ **2** x ULN (confirmed by repeat). |
| 16.1. Study-Specific Design Considerations | ….'stopping rules' have been developed for stopping treatment in the event that subjects have greater than 2 3 fold increase in **transaminases or have an increase in total bilirubin to >2 x ULN …** |
| **Rationale:** Abbreviation missing in the Time and Event Schedule section | |
| Synopsis – Time & Events schedule | **"Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire"** added below the footnotes |
| **Rationale:** Updated total blood volume to be collected (2 additional safety visits at Weeks 6 and 10) | |
| 9.1.1. Individual Stopping crieria | For each subject, the maximum amount of blood drawn in this study will not exceed ~~150~~ **200** mL |
| 16.1. Study-Specific Design Considerations | The total blood volume to be collected will not exceed ~~150~~ **200** mL |

## SYNOPSIS[a]

**A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Efficacy, Safety, and Tolerability of JNJ-42165279 in Subjects with Social Anxiety Disorder.**

JNJ-42165279 is a potent, selective, and orally bioavailable inhibitor of the enzyme fatty acid amide hydrolase (FAAH). FAAH is the enzyme primarily responsible for the degradation of a variety of fatty acid amides (FAAs), including the endocannabinoid N-arachidonoylethanolamine, or anandamide (AEA), the first identified endogenous cannabinoid receptor agonist. The endocannabinoid system is thought to play important roles in the regulation of the immune system, pain perception, and fear and anxiety responses. Modulation of fear and anxiety responses is the basis for testing JNJ-42165279 for therapeutic effect in subjects with mood disorders and clinically significant mood and anxiety symptoms.

This compound has been previously studied in six Phase 1 studies including a single ascending dose regimen up to 250 mg and a multiple dose regimen of 100 mg once-daily in healthy males, a multiple dose study with cohorts receiving 25, 75 or 100 mg for 10 days, a brain FAAH occupancy study using positron emission tomography (PET), a drug-drug interaction (DDI) study and an oral bioavailability study. A functional magnetic resonance imaging (fMRI) study with a dose of 100 mg once-daily over 4 days has recently been completed and analysis of the data is ongoing.

### OBJECTIVES AND HYPOTHESIS

#### Primary Objective

The primary objective of this study is to investigate the efficacy of JNJ-42165279 during 12 weeks of treatment in subjects with Social Anxiety Disorder (SAD).

#### Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of JNJ-42165279 in subjects with SAD.
- To assess the plasma pharmacokinetic (PK) profile of JNJ-42165279 administered as once daily (*qd)* in subjects with SAD using a population PK approach, and explore the relationship between exposure to JNJ-42165279 and efficacy and safety parameters.

#### Exploratory Objectives

The exploratory objectives are:

- To assess the efficacy of JNJ-42165279 on both anxiety and depression symptoms.
- To evaluate the impact of treatment with JNJ-42165279 compared to placebo on patient-reported assessments of symptoms of anxiety, depression, impairment in daily living and quality of life.
- To evaluate pharmacodynamic (PD) effects by the assessment of biomarkers of peripheral pharmacological activity after repeated doses of JNJ-42165279, including assessment of plasma concentrations of FAAs (anandamide AEA, palmitoylethanolamide [PEA], and oleoylethanolamide [OEA]) that are expected to rise as a consequence of the inhibition of their hydrolysis by FAAH.

[a] This section has been amended per Amendments INT-1, 2 and 3.

- To explore the relationship between plasma PK and plasma concentrations of FAAs (anandamide AEA, palmitoylethanolamide [PEA] and oleoylethanolamide [OEA]) in subjects with SAD.
- To explore any potential differences between healthy subjects and subjects with social anxiety disorder (SAD) using a population PK approach.

**Hypothesis**

JNJ-42165279 will be efficacious in reducing the symptom burden associated with SAD assessed on the Liebowitz Social Anxiety Scale (LSAS).

**OVERVIEW OF STUDY DESIGN**

This is a multi-center, double-blind, placebo-controlled, randomized, parallel-group study assessing the efficacy, safety, and tolerability of JNJ-42165279 during 12 weeks of treatment in subjects with SAD.

Approximately 137 subjects will be enrolled in this 12 week treatment study randomly assigned in a 1:1 ratio to either 25 mg of JNJ-42165279 or placebo (dosed once daily orally).

For all enrolled subjects, this study will consist of a 28-day eligibility screening period, a 12 week double-blind treatment period and a follow-up examination between 7 and 28 days after last dose. The study duration for each subject will be maximally 20 weeks.

The study will be an outpatient study.

**Screening**

After giving written informed consent, subjects may be screened over a period of up to 28 days to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study.

**Double Blind Treatment Phase**

Subjects who successfully complete the screening will visit the clinical site/unit on Day 1.

During the Treatment Phase, primarily safety and tolerability will be monitored at regular intervals (e.g. physical examination, suicidality risk assessment, vital signs, 12-lead electrocardiogram (ECG), safety labs, etc). Pharmacokinetics (plasma), and pharmacodynamic effects will be explored at the time points listed in the Time and Events Schedule.

A pharmacogenomic blood sample will be collected from all eligible subjects on Day 1. Participation in the pharmacogenomic research component is required to assess whether the subject is carrier of the A-allele variant for FAAH and to identify genetic factors that may influence the pharmacokinetics (PK), pharmacodynamics (PD), safety and/or tolerability of JNJ-42165279.

The Time and Events Schedule summarizes the visits as well as the frequency and timing of assessments applicable to this study.

**Follow Up**

Minimally 7 and maximally 28 days following last dosing (Week 12), subjects will return to the clinical site for a safety follow up visit. The procedures to be completed during the follow up visit are listed in the Time and Events Schedule.

Any serious adverse event (SAE) must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event as outlined in the protocol.

**SUBJECT POPULATION**

The target population for this study is male and female subjects with SAD who are between 18 and 64 years of age inclusive, with symptom severity as measured by the LSAS score ≥ 70 for whom pharmacotherapy is indicated.

Approximately 137 subjects with SAD will be enrolled in the proof-of-concept study to ensure 53 subjects per treatment group completing the trial, assuming a dropout rate of approximately 15%.

The inclusion and exclusion criteria for enrolling subjects in this study are described in more detail in Section 4 of the protocol.

**DOSAGE AND ADMINISTRATION**

Study medication will be provided as JNJ-42165279 tablets, strengths 25 mg and matching placebo, packaged in bottles. All tablets (JNJ-42165279 /placebo) are physically identical.

A study-site investigational product manual including instructions for dispensing, storage (on site and at home) and intake of the study medication will be supplied to the study-site.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. The sponsor may optionally develop tools to improve and/or document compliance to intake of study medication when locally feasible. This may include a diary or an electronic registration tool.

The selected 25 mg dose of JNJ-42165279 is expected to result in complete inhibition of FAAH enzyme in the brain throughout the dosing interval based on the outcome of the single ascending dose (42165279EDI1001), multiple ascending dose (42165279EDI1002) and PET occupancy (42165279EDI1003) studies.

**SAFETY EVALUATIONS**

Physical examination, neurological examination, vital signs, body weight, body temperature, clinical laboratory assessments, 12-lead ECG, urine drug screen, alcohol screening test, pregnancy testing, Columbia Suicide Severity Rating Scale (C-SSRS) assessments and evaluation of adverse events and concomitant medications will be performed during the study to monitor subject safety.

In all women, serum and urine pregnancy test will be performed at Screening and Follow-up and urine pregnancy test at study visits 2 and 9. In women of childbearing potential (WOCBP), urine pregnancy test will be performed at all other timepoints. If the urine pregnancy test is positive, a serum β-hcg test will be performed.

**PHARMACOKINETIC EVALUATIONS**

Venous blood samples for analysis of JNJ-42165279 will be collected at the time-points indicated in the Time and Events schedule.

Concentration time data will allow estimation of individual pharmacokinetic (PK) parameters for JNJ-42165279 using a population PK modeling approach. It will also help to understand potential differences between healthy subjects and subjects with SAD. Time and days of JNJ-42165279 plasma concentration assessment were chosen to gather maximal information about the PK properties of JNJ-42165279 while minimizing subject burden regarding blood sampling.

**EFFICACY EVALUATIONS**

**Primary**

*Liebowitz Social Anxiety Scale (LSAS)*

The LSAS[3] is the primary clinical scale for evaluation of the efficacy of JNJ-42165279 in SAD. It is designed to record the severity of subjective anxiety and avoidance behavior across a range of social interaction and performance situations that may be feared by a subject. It has been commonly used to study treatment outcomes in clinical trials and, more recently, to evaluate the effectiveness of cognitive-behavioral treatments.

**Secondary**

- Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A)

The SIGH-A is included here as a means to determine the frequency and severity of signs and symptoms of anxiety that maybe co-morbid with SAD and determine both their influence on treatment and their responsiveness to treatment.

- 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)

The HDRS is included as a means to determine the frequency and severity of signs and symptoms of depression that maybe co-morbid with SAD and determine both their influence on treatment and their responsiveness to treatment.

- Clinical Global Impression Improvement (CGI-I)

**Patient Reported Outcome Assessments**

Patient reported outcomes are included to assess the effect of treatment on subjective symptoms of anxiety and depression which may occur in SAD, the impact of treatment on sleep symptoms, and impairment in daily life.

- Sheehan Disability Scale (SDS)
- Generalized Anxiety Disorders (GAD-7)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Medical Outcomes Study Sleep-Revised (MOS Sleep-R)
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
- Self-Assessment of Treatment Experience

**BIOMARKER EVALUATIONS**

During the study, the following pharmacodynamics (PD) evaluations will be performed at the time points indicated in the Time and Events schedule: plasma concentrations of FAAs (AEA, PEA and OEA). Venous blood samples may be stored and used for future analysis of JNJ-42165279 metabolites and exploratory proteomics and metabolomics or other markers related to neuropsychiatric disorders.

**STATISTICAL METHODS**

*Sample Size Determination*

The sample size for the study is based on the assumption of a treatment difference of at least 10 points in the mean change from baseline to the endpoint in LSAS total score between JNJ-42165279 treatment group and placebo. A standard deviation of 24 in the change in LSAS total score from baseline is used

based on published data.[4,5,6] To detect the treatment difference of 10 points (which is judged to be clinically relevant[4,5,6]) with a power of 90% at an overall 1-sided significance level of 0.20, 53 subjects in each group are required. When adjusted for a drop-out rate of approximately 15% of subjects, the required number of subjects is 61 per treatment group. To replace 15 subjects who prematurely stopped the study when the study was put on hold, the total number of subjects entering the study will be increased from 122 to137.

*Efficacy Analysis*

All efficacy analyses will be based on the intention-to-treat (ITT) analysis set. The JNJ-42165279 treatment group will be compared with placebo using the primary efficacy endpoint, change from baseline in total LSAS score during the double-blind treatment phase.

The comparison will be performed by means of a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, JNJ-42165279) and time-by-treatment interaction as factors and baseline total LSAS score as a continuous covariate and a country and presence of comorbid major depressive disorder (MDD) as categorical covariates. Other covariates of interest may be included in the MMRM model. An unstructured variance-covariance matrix will be used. The treatment-placebo differences will be obtained using the appropriate contrast in the MMRM models at the 12-week endpoint.

The change from baseline for the secondary continuous efficacy endpoints will be analyzed in the same way as for the LSAS total score.

Sensitivity analyses of the primary endpoint will be performed using ANCOVA model; these will be detailed further in the Statistical Analysis Plan.

Descriptive statistics for values and changes from baseline (where applicable) will be provided by treatment group for all efficacy measures, including subscale scores for selected scales at each time point of the double-blind treatment phase.

Frequency tables for remission and response of social anxiety symptoms (derived from LSAS), as well as frequency tables for response of depressive and anxiety symptoms (derived from the $HDRS_{17}$ and SIGH-A) will be provided by treatment group at each time point of the double-blind treatment phase.

*Safety Analysis*

All subjects receiving at least one dose of study drug will be included in the safety analysis. All safety analyses will be performed based on the safety analysis set, which will include all randomized subjects who receive at least one dose of study drug.

*Pharmacodynamic Analysis*

Where appropriate, the relationship between plasma concentrations of JNJ-42165279 and corresponding biomarkers (plasma concentrations of FAAs [AEA, PEA, and OEA]) will be plotted to evaluate the relationships graphically. If deemed appropriate, suitable PK/PD population models will be applied to describe the exposure-effect relationships.

*Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis*

Population PK modeling of plasma concentrations of JNJ-42165279 will be undertaken. In view of the sparse sampling foreseen for this study, data may be combined with a selection of Phase 1 data (e.g. from studies 42165279EDI1001, 42165279EDI1002, and/or 42165279EDI1004) in order to support a relevant structural model.

Population PK/PD analysis of biomarkers and/or efficacy markers may also be performed, and a suitable dose- and/or exposure-response model may be developed. If necessary or relevant for the analysis, Phase 1 data may be integrated to inform the model structure or key parameter values.

## TIME AND EVENTS SCHEDULE[a]

| Phase | Screening | Double-Blind Treatment[a] | | | | | | | | Posttreatment[b] (Follow up) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | EW[b] | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| **Week (end of)** | **-4 to 0** | **0** | **1** | **2** | **4** | **6** | **8** | **10** | **12** | **13 to 16** |
| **Day** | **-28 to -1** | **1** | **7** | **14** | **28** | **42** | **56** | **70** | **84** | **91 to 112** |
| **Clinic Visit (C)** | C | C | C | C | C | C | C | C | C | C |
| **Study Procedures** | | | | | | | | | | |
| Screening/Administrative | | | | | | | | | | |
| Informed consent (including pharmacogenomics) | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | |
| Prestudy therapy [c] | X | | | | | | | | | |
| Preplanned surgery/procedure(s) | X | | | | | | | | | |
| MINI interview | X | | | | | | | | | |
| Study Drug Administration | | | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Dispense JNJ-42165279 or placebo | | X | | | X | | X | | | |
| Optional: diary/tool to document drug intake | | continuous | | | | | | | | |
| Drug accountability | | | X | X | X | | X | | X | |
| Safety Assessments | | | | | | | | | | |
| Physical examination | X | | | | | | | | X | X |
| Neurological examination [t] | X | | | | X | | X | | X | |
| C-SSRS | X[p] | X | X | X | X | X | X | X | X | |
| Vital signs[e] | X | X | X | X | X | | X | | X | X |
| Body temperature | X | X | X | X | X | | X | | X | X |
| Body weight [f] | X | X | | | X | | | | X | X |
| Height | X | | | | | | | | | |
| Clinical laboratory assessments[g] | X | X | | X | X | X | X | X | X | X[h] |
| Serology | X | | | | | | | | | |
| 12-lead ECG [i] | X | X[d] | | | X | | | | X | X[h] |

[a] This section has been amended per Amendments INT-1, 2 and 3.

| Phase | Screening | Double-Blind Treatment[a] | | | | | | | | Posttreatment[b] (Follow up) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | EW[b] | |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Week (end of) | -4 to 0 | 0 | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 13 to 16 |
| Day | -28 to -1 | 1 | 7 | 14 | 28 | 42 | 56 | 70 | 84 | 91 to 112 |
| Clinic Visit (C) | C | C | C | C | C | C | C | C | C | C |
| Urine drug screen | X[j] | X | | | X | | | | X | |
| Alcohol screen | X | X | | X | X | | X | | X | X[h] |
| Pregnancy test | X[k] | X[k] | X[u] | X[u] | X[u] | X[u] | X[u] | X[u] | X[k] | X[k] |
| Clinician-administered assessments | | | | | | | | | | |
| Liebowitz Social Anxiety Scale (LSAS) | X | X | X | X | X | | X | | X | |
| $HDRS_{17}$ using SIGH-D – performed by clinical site[q] | X | X | X | X | X | | X | | X | |
| SIGH-A (includes $HAM\text{-}A_6$)[l] - performed by clinical site | | X | X | X | X | | X | | X | |
| CGI-I | | | X | X | X | | X | | X | |
| Patient-reported assessments | | | | | | | | | | |
| Sheehan Disability Scale | | X | | | X | | X | | X | |
| GAD-7 | | X | | | X | | X | | X | |
| SHAPS | | X | | | X | | X | | X | |
| MOS Sleep-R | | X | | | X | | X | | X | |
| Q-LES-Q | | X | | | X | | X | | X | |
| Self-assessment of treatment experience | | | | | | | | | X | |
| Pharmacokinetics | | | | | | | | | | |
| Blood sample collection for JNJ-42165279[m] | | | | X | X | | | | | |
| Pharmacogenomics (DNA) | | | | | | | | | | |
| Blood sample collection for pharmacogenomics[n] | | X | | | | | | | | |
| Biomarkers | | | | | | | | | | |
| Blood sample collection for FAAs[o] | | X | | | X | | | | X | |
| Ongoing Subject Review | | | | | | | | | | |
| Behavioral guidance[r] | *Continuous* | | | | | | | | | |
| Concomitant therapy[s] | *Continuous* | | | | | | | | | |
| Adverse events | *Continuous* | | | | | | | | | |

Footnotes:

a. Visits should be conducted within +/-3 days of the scheduled day.
b. If a subject discontinues treatment before the end of the double-blind treatment phase, early withdrawal (EW) and post-treatment assessments should be obtained. Follow-up visit will take place 7 to 28 days after last dose intake or early withdrawal.
c. Prestudy therapy will include all medications taken within the 30 days before screening.
d. Triplicate ECG at Day 1
e. Supine blood pressure, pulse, and oral temperature. Following the supine vital sign assessment, orthostatic vital signs (blood pressure, pulse) will be taken after standing for at least 3 minutes.
f. Body weight will be measured with subjects lightly clothed.
g. Serum chemistry, hematology, coagulation and urinalysis.
h. Only in case of any clinical significant abnormalities observed at Week 12.
i. ECG should be performed prior to study drug administration, and if possible, at approximately the same time of the day as the screening ECG.
j. Refer to study exclusion criteria for circumstances in which a repeat test during Screening is permitted.
k. Performed for all women. Serum and urine pregnancy test performed at Screening and Follow-up. At all other time points, if the urine pregnancy test is positive, a serum β-hcg test will be performed. Investigators may perform additional pregnancy testing at their discretion as clinically needed.
l. The HAM-$A_6$ is a subscale derived from the SIGH-A (structured interview guide version of the HAM-A).
m. At each time point, a venous blood sample will be collected for PK analysis of JNJ-42165279 concentration at predose (i.e., prior to morning dose on Days 14 and 28) and 2 hours postdose (only at Day 14).
n. A 10 mL blood sample will be collected for the pharmacogenomics component of this study. A sample collected at a later time point does not constitute a protocol violation and would not require protocol amendment.
o. A venous blood sample will be collected for the FAAs (AEA, PEA and OEA) and exploratory biomarkers. The Visit 2 sample must be taken before the first dose of JNJ-42165279 /placebo.
p. Baseline version completed at Screening.
q. $HDRS_{17}$ anxiety/somatization factor score determined from the assessment.
r. Behavioral guidance from the investigator: at the beginning of the trial subjects will be advised to enter socially feared situations to help determine whether the treatment has beneficial or adverse effects on symptoms and behaviors and then at subsequent visits the investigator will query the subject about social situations that s/he has encountered since the last visit, and how s/he felt in those situations.
s. Concomitant therapies must be recorded throughout the study beginning with signature of the ICF to the final follow up visit (Visit 8).
t. A neurological examination will also be completed in case of adverse event of interest.
u. Urine pregnancy test in WOCBP only. If the urine pregnancy test is positive, a serum β-hcg test will be performed. Investigators may perform additional pregnancy testing at their discretion as clinically needed.

**CGI-I**=Clinical Global Impression – Improvement; **C-SSRS** = Columbia Suicide Severity Rating Scale; **EW** = Early Withdrawal; **GAD-7** = Generalized Anxiety Disorders ;**HAM-$A_6$** = Hamilton Anxiety Rating scale; **$HDRS_{17}$** = Hamilton Depression Rating Scale; **LSAS** = Liebowitz Social Anxiety Scale; **MINI** = Mini International Neuropsychiatric Interview; **MOS Sleep-R** = Medical Outcomes Study Sleep-Revised; **Q-LES-Q =** Quality of Life Enjoyment and Satisfaction Questionnaire; **SHAPS** = Snaith-Hamilton Pleasure Scale**; SIGH-A** = Structured Interview Guide for the Hamilton Anxiety Scale; **SIGH-D**= Structured Interview Guide for the Hamilton Depression Scale

## ABBREVIATIONS

Note: Pharmacokinetic Parameters are defined in Section 9.5.3 and questionnaires are defined after the Time and Events Schedule.

| | |
|---|---|
| AEA | anandamide |
| ALP | alkakine phosphatase |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | Aspartate transaminase |
| BMI | Body mass index |
| CI | Confidence interval |
| CPK | Creatine phosphokinase |
| CSF | Cerebrospinal fluid |
| CYP | cytochrome P450 |
| DDI | Drug-Drug Interaction |
| DRC | Data Review Committee |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders (5$^{th}$ edition) |
| ECG | electrocardiogram |
| ED | Effective Dose |
| (e)CRF | (electronic) case report form |
| eDC | Electronic data capture |
| FAAH | Fatty acid amide hydrolase |
| FAAs | Fatty acid amides |
| FDA | Food and Drug Administration |
| fMRI | Functional magnetic resonance imaging |
| GAD | Generalized anxiety disorder |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GGT | Gamma-glutamyltransferase |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C antibodies |
| hERG | Human Ether-à-go-go-Related Gene |
| HIV | Human immunodeficiency virus |
| IB | Investigators Brochure |
| IC | Inhibitory Concentration |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| ITT | Intention-to-Treat |
| IEC | Independent Ethics Committee |
| LC-MS/MS | Liquid chromatography/mass spectrometry/mass spectrometry |
| LDH | Lactic acid dehydrogenase |
| MAD | Multiple Ascending Dose |
| MDD | Major Depressive Disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| NOAEL | no-observed-adverse-effect-level |
| OEA | Oleoylethanolamide |
| PD | Pharmacodynamics |
| PEA | Palmitoylethanolamide |
| PET | Positron emission tomography |
| PK | Pharmacokinetic |
| PQC | Product Quality Complaint |
| q.d. | Once-daily |
| RBC | Red blood cell |
| SAD | Social anxiety disorder |
| SAE | Serious adverse event |
| SD | Standard deviation |
| TEAE | Treatment emergent adverse event |
| ULN | Upper Limit of Normal |
| Vss | Volume of distribution at steady state |
| WBC | White blood cell |
| WOCBP | Women of child bearing potential |

# 1. INTRODUCTION

JNJ-42165279 is a potent, selective, and orally bioavailable inhibitor of the enzyme fatty acid amide hydrolase (FAAH). FAAH is the enzyme primarily responsible for the degradation of a variety of fatty acid amides (FAAs), including the endocannabinoid N-arachidonoylethanolamine, or anandamide (AEA), the first identified endogenous cannabinoid receptor agonist. The endocannabinoid system is thought to play important roles in the regulation of the immune system, pain perception, and fear and anxiety responses. Modulation of fear and anxiety responses is the basis for testing JNJ-42165279 for therapeutic effect in subjects with mood disorders and clinically significant mood and anxiety symptoms.

This compound has been previously studied in six Phase 1 studies including a single ascending dose regimen up to 250 mg and a multiple dose regimen of 100 mg once-daily in healthy males, a multiple dose study with cohorts receiving 25, 75 or 100 mg for 10 days, a brain FAAH occupancy study using positron emission tomography (PET), a drug-drug interaction (DDI) study and an oral bioavailability study. A functional magnetic resonance imaging (fMRI) study with a dose of 100 mg once-daily over 4 days has recently been completed and analysis of the data is ongoing.

For the most comprehensive nonclinical and clinical information regarding JNJ-42165279, refer to the latest version of the Investigator's Brochure (IB) for JNJ-42165279.[1]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

## 1.1. Background

**Nonclinical Studies**

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of JNJ-42165279, refer to the latest version of the IB for JNJ-42165279.[1]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

**Nonclinical Pharmacology**

JNJ-42165279 is a mechanism-based inhibitor of FAAH (IC50s of 26 ±4.9 nM [human] and 500 ± 70 nM [rat] at native FAAH) with behavior consistent with a slowly turned-over enzyme substrate. Extensive in vitro profiling, including Cerep and kinase panels, radioligand binding, functional assays, and proteomics studies, has shown this compound to be highly selective.

Efficacy has been demonstrated in three in vivo pain models in rats: the mild thermal injury model of acute burn pain, the formalin paw model of tonic pain, and the spinal nerve ligation model of neuropathic pain. Doses that produced maximal FAAH enzyme inhibition in white blood cells (WBCs) and brain corresponded to doses that produced maximal efficacy in the spinal nerve ligation model of neuropathic pain. Efficacy with JNJ-42165279 has also been demonstrated in the stress-induced anorexia rat model of anxiety. The estimated human

efficacious plasma concentration (80 ng/mL, 0.2 μM) was derived from the $ED_{90}$ in the rat spinal nerve ligation model corrected for the 20-fold difference in human versus rat $IC_{50}$ in the whole blood FAAH inhibition assay. This estimate is used for safety margin calculations in the rest of this document.

**Safety Pharmacology**

JNJ-42165279 had no adverse effect at 1 μM in the human ether-a-go-go related gene (hERG) patch clamp assay ($IC_{50}$ = 27 μM) and at 10 μM (the maximal dose assessed) in the rabbit Purkinje fiber assay.

In the Good Laboratory Practice (GLP) male conscious dog cardiovascular safety study, oral doses up to 25 mg/kg ($C_{max}$ = 6,628 ng/mL; 83-fold margin over the projected efficacious dose in humans of 80 ng/mL) did not induce relevant changes in cardiovascular, electrocardiographic, or respiratory parameters. At the highest dose of 150 mg/kg (mean plasma exposure of 8,418 ng/mL), a 40% increase in heart rate was observed in one dog, and a 23% prolongation of the QTcF interval in another. No other relevant changes were recorded in the other cardiovascular, electrocardiographic, or respiratory parameters. There were no meaningful effects in the anesthetized guinea pig model.

In the neurobehavioral (Irwin) safety assessment study in rats, dose-related decreased body temperature and decreases in motor function were noted from 25 to 500 mg/kg, with changes in sensory-motor and affective responses at 500 mg/kg.

**Pharmacokinetics and Product Metabolism in Animals**

JNJ-42165279 has moderate to high oral bioavailability in rats (37 to 113%), dogs (57 to 109%), and monkeys (119%). After intravenous administration, clearance was low in the dog and monkey (6 and 11 mL/min/kg, respectively) and high in the rat (60 mL/min/kg); the volume of distribution at steady state (Vss) was moderate (1.1 L/kg to 2.5 L/kg); and the half-life ranged from 1.1 to 3.2 hours. JNJ-42165279 was highly bound (90% to 97%) to plasma proteins in all species with the highest binding in the dog. Brain-to-plasma ratios were consistent over time in the rat, and ranged from 1.3 to 1.9 in the rat and 0.6 to 1.8 in the dog.

JNJ-42165279 is primarily metabolized by cytochrome P450 (CYP)3A4 in liver microsomes with multiple metabolites observed in vitro and in vivo. All metabolites formed in human hepatocytes or human liver microsomes were also detected in vitro or in vivo in the toxicology species investigated, with the exception of the di-oxidation metabolite M9, which was detected in human hepatocytes only. Currently no information is available about any pharmacology of any metabolites of JNJ-42165279.

**Toxicology**

The oral toxicity of JNJ-42165279 was characterized in 3-month toxicity studies in rats and dogs. In male rats at all doses, adverse effects on coagulation parameters (increased prothrombin time [PT] and activated partial thromboplastin time [aPTT]) and the reproductive organs (decreased sperm motility and abnormal sperm morphology) were observed. In female rats,

microscopic changes were observed in the kidney (mineralization and vacuolar degeneration) at ≥25 mg/kg, while there were no findings at the low dose of 5 mg/kg. Based on these findings, the no observed adverse effect level (NOAEL) could not be established in male rats and was 5 mg/kg in female rats. Relative to exposures at the anticipated clinically effective dose of 25 mg (Day 10 $C_{max}$= 225 ng/mL and AUC = 2,204 ng.h/mL), $C_{max}$ and AUC exposures in the female rats provide 10-fold and 3.5-fold margins respectively. In dogs, doses of 5 and 15 mg/kg were well tolerated, while adverse effects at 100→50 mg/kg were noted in the liver and gall bladder (vacuolation with cellular degeneration or necrosis that correlated with mild increases in aspartate transaminase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and gamma-glutamyltransferase [GGT]), thymus (atrophy), bone (hypercellularity of the erythroid cell line in sternal bone marrow), and epididymis/testis (decreased sperm numbers and secondary spermatid degeneration/depletion). Based on these findings, the NOAEL in dogs was 15 mg/kg, providing $C_{max}$ and AUC margins of at least 26-fold and 35-fold over those at the anticipated human effective levels.

Reproductive and embryo-fetal safety was evaluated in rats and rabbits. Male rats treated with JNJ-42165279 for 4 weeks had significantly reduced sperm motility and increased number of abnormal sperm at doses of 100 and 200 mg/kg but not at 25 mg/kg; these changes were fully reversible following a 4-week recovery period. JNJ-42165279 at the high dose of 100 mg/kg, but not at ≤30 mg/kg, induced changes in female rat oestrus cycling (regularity and cycle length). These changes as well as those on sperm motility are considered exaggerated effects of FAAH inhibition. The $C_{max}$ (3,280 ng/mL) and AUC (13,900 ng.h/mL) exposures in male rats at 25 mg/kg (the NOAEL for fertility findings) provide margins of 14.6- and 6-fold over the anticipated human effective levels. In pregnant rats and rabbits, JNJ-42165279 induced minimal maternal toxicity (decreased food consumption and body weight gain). There were no fetal changes in rabbits. In rabbits, the NOAEL for fetal toxicity was the highest dose tested, offering $C_{max}$ and AUC margins of over 78-fold. Rat fetuses from pregnant rats treated with ≥30 mg/kg during the period of organogenesis (gestation Days 6-17) showed a dose-related increase in incidence of primary lens fiber degeneration which translated to an increased incidence of nuclear cataracts in young adult offspring from treated pregnant dams. Primary lens fiber degeneration and nuclear cataracts are common background findings in the Sprague Dawley rat strain used in these studies but their incidence was exacerbated by treatment with JNJ-42165279. A NOAEL was established at 10 mg/kg and associated exposures provide $C_{max}$ and AUC margins of 16- and 9-fold respectively. No lens changes were reported in adult rats and dogs treated with JNJ-42165279 daily for up to 3-months.

JNJ-42165279 was not genotoxic in the in vitro bacterial/microsomal activation assay, the mouse lymphoma assay, or the in vivo chromosome aberration test in rats.

**Clinical Studies**

This will be the seventh study involving the administration of JNJ-42165279 to humans.

A double-blind Phase 1 study (Study 42165279EDI1001) was completed with 29 healthy male subjects to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic (PD)

activity of JNJ-42165279 after single and repeated oral dosing. In Part 1, two cohorts (both n=9) received single ascending doses of JNJ-42165279 or placebo during each of 3 or 4 dosing periods, separated by washout periods, using an alternating panel design. Two additional subjects participated in Panel 1 but withdrew from the study after the first dosing for reasons unrelated to safety or tolerability; 1 received placebo and 1 received JNJ-42165279.

Doses studied in a fasted state were 2.5, 10, 30, 100, 175, and 250 mg. An additional 30-mg dose was also administered after intake of a regular meal. In Part 2, a separate cohort of 9 subjects received either 100 mg JNJ-42165279 (n=6) or placebo (n=3) once-daily for 6 consecutive days in a fed state. JNJ-42165279 was administered as an oral suspension (5 mg/mL or 50 mg/mL) throughout the study.

After a single dose, systemic exposure to JNJ-42165279, expressed as $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$, increased with increasing dose. Plasma JNJ-42165279 concentrations declined in a multi-exponential manner, with mean $t_{1/2}$ values of 4.84 to 14.4 hours for doses of 2.5 to 250 mg.

The effect of concomitant food intake on the pharmacokinetics of JNJ-42165279 was investigated at the 30-mg dose level. The rate of absorption was delayed based on median $t_{max}$ values of 2.25 hours and 0.5 hours in the fed and fasted states, respectively. On average, the $C_{max}$ values were 33% lower and $AUC_{\infty}$ values were 16% higher when JNJ-42165279 was given with food, relative to administration in the fasted state. These apparent effects of food are not expected to be clinically significant.

JNJ-42165279 $C_{max}$ was reached at 0.5 to 2.5 hours postdose (median $t_{max}$ value, 0.75 hours) following single-dose and once-daily administration of 100 mg. Based on the trough (i.e., predose) concentrations, steady-state conditions were achieved by the third 100-mg daily dose of JNJ-42165279. On average, the $C_{max}$ and $AUC_{\tau}$ values were 1.13-times and 1.44-times higher on Day 6 relative to Day 1. The similarity between the mean $AUC_{\infty}$ following the 100-mg dose during Part 1 (8,419 ng.h/mL) and the mean $AUC_{\tau}$ on Day 6 during Part 2 (8,644 ng.h/mL) further suggests that the pharmacokinetics of JNJ-42165279 is consistent after single-dose and once-daily repeated administration.

At a dose level of 30 mg or higher, FAAH activity in white blood cells (WBCs) showed a significant decrease with duration of at least 24 hours. At the same time the FAA plasma levels showed a significant increase.

JNJ-42165279 was found to be well tolerated. There were no clinically significant changes in any safety measurements, including clinical laboratories, electrocardiograms (ECGs), vital signs, and physical and neurological examinations. There were no changes or abnormal findings in blood coagulation parameters. There were no deaths, serious adverse events, or discontinuations due to adverse events. All adverse events reported were mild in severity and had resolved by the time of the follow-up visit. The most frequently reported adverse events for subjects receiving JNJ-42165279 were headache, nasal congestion, and dizziness.

In the second multiple ascending dose (MAD) study 42165279EDI1002, four cohorts were studied: healthy males at 25 mg and 75 mg; healthy females (non-child bearing potential) at 100 mg, and healthy elders at 100 mg. Six subjects were on active and two on placebo in each cohort. All subjects were dosed during 10 days. Concentrations of JNJ-42165279 in plasma, urine, and cerebrospinal fluid (CSF) were measured; and FAAH activity in leucocytes (WBCs), and anandamide (AEA), N-oleoylethanolamide (OEA), N-palmitoylethanolamide (PEA) in plasma, and AEA, OEA, and arachidonic acid (AA) in CSF were assayed. Tolerability, including effects on cognition and subjective ratings, were assessed. As dose related increases in coagulation parameters had been observed in male rats, blood coagulation parameters were also included.

A preliminary analysis of data from study 42165279EDI1002 indicates that the plasma pharmacokinetics of JNJ-42165279 in female subjects and elderly subjects are similar to each other and to healthy male subjects enrolled in study 42165279EDI1001. These 3 subject groups received a single 100-mg dose of JNJ-42165279 and once-daily administration of the same dose until steady-state conditions were achieved.

Pharmacodynamic measures revealed that across the 25- to 100-mg JNJ-42165279 dose range, FAAH activity in WBCs was suppressed attaining a mean nadir of 7.85% to 10.4% (relative to predose values) after a single dose and a mean nadir of 0.58% to 10.5% after once-daily dosing for 10 days. At 96 hours after the last dose, mean FAAH activity remaining ranged from 28.3% to 58.2% of predose values. Single doses of JNJ-42165279 in the range of 25 to 100 mg produced mean peak concentrations of AEA in plasma that were 5.5- to 10-times higher than mean predose values, whereas mean peak OEA and PEA concentrations 4.3- to 5.6-times higher. Similar changes in mean FAA concentrations were observed after daily administration of 25 to 100 mg for 10 days. Mean plasma AEA, OEA, and PEA concentrations were 1.3- to 3.1-times higher than mean predose values at 96 hours after the last JNJ-42165279 dose. Daily administration of JNJ-42165279 for 7 days increased mean AEA and OEA concentrations in CSF by approximately 41-times and 5.8-times (25 mg dose), respectively, and 77-times and 7.4-times (75 mg dose), respectively, relative to predose. The concentrations of AA in CSF were unchanged.

The most common treatment emergent adverse events (TEAEs) (≥3 subjects per dose group) in subjects dosed with JNJ-42165279 were headache, dizziness, and fatigue. Overall, more TEAEs were reported with JNJ-42165279 compared with placebo. All the TEAEs were either mild or moderate in intensity. None of the TEAEs was reported as severe and all were considered by the investigator as either doubtfully related or possibly related to the study drug. There were four TEAEs of hepatic enzymes elevated. One subject taking placebo, one woman of non-child bearing potential, and two healthy elderly subjects taking 100 mg JNJ-42165279, had transient elevations of liver transaminases relative to baseline (up to 2.5 times the upper limit of normal) that returned to normal after dosing stopped. No increases occurred in alkaline phosphatase (ALP) or bilirubin. No such increases were observed in the 25 mg cohort. There were no clinically significant changes in any safety measurements, including clinical laboratories, ECGs, vital signs, and physical and neurological examinations. There were no changes or abnormal

findings in blood coagulation parameters. There were no deaths, serious adverse events, or discontinuations due to adverse events. Subjects receiving 100 mg reported slight similarity to sedatives and dissimilarity to stimulants on the Addiction Research Center Inventory-53; no groups reported similarity to cannabinoids. No subjective effects were reported in any of the cohorts by Bond-Lader visual analogue scales.

During the DDI study 42165279EDI1004 sixteen subjects received a single 30-mg JNJ-42165279 dose on Day 1. Thereafter, they received single oral doses of 200-mg itraconazole from Day 4 to Day 10 (inclusive). Subjects also received a dose of 30-mg JNJ-42165279 along with 200 mg itraconazole on Day 8.

Mean plasma JNJ-42165279 concentrations were greater over the entire PK sampling period after co-administration of JNJ-42165279 with itraconazole, compared with administration of JNJ-42165279 alone. Plasma JNJ-42165279 concentrations increased rapidly, with median $t_{max}$ values of 1.00 hour following administration of JNJ-42165279 with and without itraconazole.

Mean $t_{1/2}$ was approximately 196% longer after JNJ-42165279 was co-administered with itraconazole, compared with JNJ-42165279 administered alone. The estimated geometric mean ratios (GMRs) of JNJ-42165279 $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$ for the co-administered treatment relative to JNJ-42165279 administered alone were 136%, 373%, and 447%, respectively. These results indicate that CYP3A4 plays an important role in the metabolic elimination of JNJ-42165279 and that inhibition of this enzyme by potent inhibitors is expected to result in an increase in the concentrations of JNJ-42165279 in plasma.

An analysis of brain FAAH occupancy by JNJ-42165279 using PET of $^{11}$C-MK-3168 has been conducted (study 42165279EDI1003). Analyses of PET scans after single doses of JNJ-42165279 ranging from 2.5 mg to 50 mg indicate that significant (85% to 95%) occupancy of FAAH in brain can be seen after pretreatment with doses as low as 10 mg and occupancy is completely saturated after higher doses. Other analyses including PK of JNJ-42165279 and inhibition of FAAH activity in leukocytes at the time of brain occupancy measurements are ongoing.

A fMRI study with a dose of 100 mg once-daily over 4 days in healthy young males has recently been completed and analyses of the data are in progress.

For more details about the Phase 1 clinical data please refer to the IB.[1]

## 1.2. Overall Rationale for the Study

The endocannabinoid system is thought to play important roles in the regulation of the immune system, pain perception, and fear and anxiety responses. Modulation of fear and anxiety responses is the basis for testing JNJ-42165279 for therapeutic effect in subjects with mood disorders and clinically significant mood and anxiety symptoms. Social anxiety disorder (SAD) is among the most common anxiety disorders and is associated with significant distress and dysfunction in affected individuals. A number of treatments have been tested for SAD including SSRIs and other antidepressants, benzodiazepines, and pregabalin as well as cognitive and

behavioral treatments. Each of these has strengths and limits, most notably poor tolerance to sexual adverse effects associated with SSRIs and other antidepressants, and sedation and risk for tolerance and abuse with benzodiazepines. Moreover, many subjects with SAD do not respond or respond poorly to available treatments and remain symptomatic (Pollock et al 2014)[4]. There continues to be a need for effective, safe, and well tolerated treatments.

# 2. OBJECTIVES AND HYPOTHESIS

## 2.1. Objectives

**Primary Objective**

The primary objective of this study is to investigate the efficacy of JNJ-42165279 during 12 weeks of treatment in subjects with SAD.

**Secondary Objectives**

The secondary objectives of this study are:

- To assess the safety and tolerability of JNJ-42165279 in subjects with SAD.
- To assess the plasma pharmacokinetic (PK) profile of JNJ-42165279 administered as once daily (*qd)* in subjects with SAD using a population PK approach, and explore the relationship between exposure to JNJ-42165279 and efficacy and safety parameters.

**Exploratory Objectives**

The exploratory objectives are:

- To assess the efficacy of JNJ-42165279 on both anxiety and depression symptoms.
- To evaluate the impact of treatment with JNJ-42165279 compared to placebo on patient-reported assessments of symptoms of anxiety, depression, impairment in daily living and quality of life.
- To evaluate pharmacodynamic (PD) effects by the assessment of biomarkers of peripheral pharmacological activity after repeated doses of JNJ-42165279, including assessment of plasma concentrations of FAAs (anandamide AEA, palmitoylethanolamide [PEA], and oleoylethanolamide [OEA]) that are expected to rise as a consequence of the inhibition of their hydrolysis by FAAH.
- To explore the relationship between plasma PK and plasma concentrations of FAAs (anandamide AEA, palmitoylethanolamide [PEA] and oleoylethanolamide [OEA]) in subjects with SAD.
- To explore any potential differences between healthy subjects and subjects with social anxiety disorder (SAD) using a population PK approach.

## 2.2. Hypothesis

JNJ-42165279 will be efficacious in reducing the symptom burden associated with SAD assessed on the Liebowitz Social Anxiety Scale (LSAS).

# 3. STUDY DESIGN AND RATIONALE

## 3.1. Overview of Study Design[a]

This is a multi-center, double-blind, placebo-controlled, randomized, parallel-group study assessing the efficacy, safety, and tolerability of JNJ-42165279 during 12 weeks of treatment in subjects with SAD.

Approximately one-hundred thirty-seven (137) subjects will be enrolled in this 12 week treatment study randomly assigned in a 1:1 ratio to either 25 mg of JNJ-42165279 or placebo (dosed once daily orally).

For all enrolled subjects, this study will consist of a 28-day eligibility screening period, a 12 week double-blind treatment period and a follow-up examination between 7 and 28 days after last dose. The study duration for each subject will be maximally 20 weeks.

The study will be an outpatient study.

**Screening**

After giving written informed consent, subjects may be screened over a period of up to 28 days to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study.

**Double Blind Treatment Phase**

Subjects who successfully complete the screening will visit the clinical site/unit on Day 1.

During the Treatment Phase, primarily safety and tolerability will be monitored at regular intervals (e.g. physical examination, suicidality risk assessment, vital signs, 12-lead ECG, safety labs, etc). Pharmacokinetics (plasma), and pharmacodynamic effects will be explored at the time points listed in the Time and Events Schedule.

A pharmacogenomic blood sample will be collected from all eligible subjects on Day 1. Participation in the pharmacogenomic research component is required to assess whether the subject is carrier of the A-allele variant for FAAH and to identify genetic factors that may influence the pharmacokinetics (PK), pharmacodynamics (PD), safety and/or tolerability of JNJ-42165279.

The Time and Events Schedule summarizes the visits as well as the frequency and timing of assessments applicable to this study.

[a] This section has been amended per Amendment INT-3.

**Follow Up**

Minimally 7 and maximally 28 days following last dosing (Week 12), subjects will return to the clinical site for a safety follow up visit. The procedures to be completed during the follow up visit are listed in the Time and Events Schedule.

Any serious adverse event (SAE) must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event as outlined in the protocol.

## 3.2. Study Design Rationale[a]

**Randomization, Blinding, Control, Study Phase/Periods, Treatment Groups**

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints as well as adverse events. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

**Population**

The target population for this study is male and female subjects with SAD who are between 18 and 64 years of age inclusive, with symptom severity as measured by the Liebowitz Social Anxiety Scale score $\geq$ 70 for whom pharmacotherapy is indicated. Subjects with SAD frequently have additional comorbid anxiety disorders notably Generalize Anxiety Disorder (GAD), major depressive disorders (MDD), and substance use disorders. To determine whether comorbid conditions influence the response to JNJ-42165279, and whether JNJ-42165279 has effects across anxiety and depression as a behavioral dimension, subjects with comorbid MDD and generalized anxiety disorder (GAD) will be allowed to participate provided that SAD is judged by the investigator to be the primary indication for treatment. Subjects experiencing a current episode of MDD severe enough to warrant treatment of depression as the primary focus will be excluded.

Given the observation in the rat reproductive toxicology studies (see Section 1.1), WOCBP will only be included if they agree to ongoing use of a highly effective method of birth control (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly). All WOCBP will have a pregnancy test at screening, each study visit and at follow-up. WOCBP constitute a large part of the target population in clinical practice. Safety and efficacy data in this population are important for future clinical studies.

[a] This section has been amended per Amendment INT-3.

**Trial Duration**

12 weeks has been the duration of numerous randomized placebo controlled trials of the effectiveness of a monotherapy for SAD (Stein DJ et al 2009: Cochrane review article) and is supported by the observation from trials of paroxetine, that non-responders at 8 weeks of treatment could still demonstrate response after 12 weeks of treatment (Stein DJ, Stein MB, Pitts CD, Kumar R, Hunter B. Predictors of response to pharmacotherapy in social anxiety disorder: An analysis of 3 placebo-controlled paroxetine trials. Journal of Clinical Psychiatry 2002:63(2):152–5)[6]. Due to the chronic and recurrent nature of mood and anxiety disorders, treatment studies of longer duration will be required if this compound demonstrates acceptable safety and efficacy for at least 12 weeks.

**Rationale for Dose Selection**

Modeling based on nonclinical pain models (with adjustment for differences in affinity of JNJ-42165279 for human FAAH) yielded an estimate of the exposure needed to provide 90% maximal effect of 80 ng/mL (see the Investigator's Brochure), and is hypothesized to be a function of complete (>90%) inhibition of FAAH. Modeling of steady state concentrations based on the single ascending dose and multiple ascending dose studies predict that exposures above 80 ng/ml will be reached by the majority of the subjects at steady state while taking 25 mg and sustained for at least 6 hours after dosing. The covalent binding of JNJ-42165279 to FAAH and slow hydrolysis from the enzyme catalytic site should result in inhibition to be sustained throughout the dosing interval resulting in a longer pharmacodynamic half-life. Sustained occupancy of FAAH in the brain was confirmed in the $^{11}$C-MK3168 PET study 42165279EDI1003. Occupancy following 10 mg was identical at $C_{max}$ and trough at steady state. In the periphery, suppression of FAAH activity in WBC was also sustained throughout the dosing interval during chronic dosing at 25 mg in study 42165279EDI1002. In the same study, increases in FAA concentrations in cerebrospinal fluid (CSF) were observed after 7 days of dosing with 25 mg. The dose of 75 mg was observed to generate greater increases (77-times for AEA and 7.4-times for OEA) in median CSF FAA concentrations although the range of effect substantially overlapped with that occurring after 7 days dosing with 25 mg (41-times for AEA and 5.8 times for OEA). Substantial blocking of retention of the Merck FAAH tracer $^{11}$C-MK3168 in brain was observed in human PET studies after pretreatment with single doses of 10 mg (80 to 95% occupancy). The occupancy curve was asymptotic (>95%) with higher doses (25 and 50 mg) of JNJ-42165279. In study 42165279EDI1002, doses of 100 mg were associated with mild, reversible increases in liver transaminases in a few subjects while no such effects were observed in subjects taking 25 and 75 mg. Based on these results, 25 mg JNJ-42165279 is predicted to consistently result in > 95% inhibition of FAAH activity without significant variability throughout the day and can provide robust pharmacodynamic effects. While slightly larger effects on CSF FAA turnover were seen with 75 mg, the dose of 25 mg offers a better safety margin given that exposures of JNJ-42165279 can increase (up to 4 fold in AUC) in the presence of strong CYP3A4 inhibitors.

## Rationale for Clinical Endpoints

### Primary

*Liebowitz Social Anxiety Scale (LSAS)*

The Liebowitz Social Anxiety Scale (LSAS) was developed in 1987 by Michael Liebowitz (Liebowitz MR. Social Phobia. Mod Probl Pharmacopsychiatry 1987;22:141-173)[3]. It is a short questionnaire with 24 items, 13 relating to performance anxiety and 11 concerning social situations. The LSAS is designed to record subjective anxiety across a range of social interaction and performance situations that may be feared by a subject. The responses to these situations and associated avoidance behavior reported by the subject can be used to assist in the diagnosis of social anxiety disorder, assess severity, and monitor change. It has been commonly used to study treatment outcomes in clinical trials and, more recently, to evaluate the effectiveness of cognitive-behavioral treatments. An example of the LSAS is provided in Attachment 6.

### Secondary

Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A)

*The SIGH-A is included here as a means to determine the frequency and severity of signs and symptoms of anxiety, including subjects with comorbid GAD and MDD, and determine both their influence on treatment and their responsiveness to treatment.*

This original HAM-A scale assesses the severity of different anxiety-related symptoms (Hamilton 1959[13]; Hamilton 1969[16]). As the original HAM-A lacks instructions for administration and clear anchor points for the assignment of severity ratings, the structured interview guide version will be used in the current study (Shear 2001)[20]. The SIGH-A has been shown to have high inter-rater and test-retest reliability and produced similar but consistently higher (+ 4.2) scores compared to the original HAM-A. Correlation with a self-report measure of overall anxiety has also been shown to be high (Shear 2001)[20]. Subscales, such as the HAM-$A_6$ which focuses on psychic anxiety and may be more sensitive to certain treatments, can be derived from the SIGH-A.

*Hamilton Depression Rating Scale ($HDRS_{17}$)*

*Depression scales are included here as a means to determine the frequency and severity of signs and symptoms of depression that maybe co-morbid with SAD and determine both their influence on treatment and their responsiveness to treatment.*

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in subjects diagnosed with depression (Hamilton M 1960)[14] with a score range of 0 to 52. It is the most widely used symptom severity measure for depression. Each of the 17 items is rated by the clinician on either a 3- or a 5-point scale. The HDRS has an inter-rater reliability correlation of r = .90 and the internal consistency of the measure is reported to be high with a coefficient alpha of 0.88. Criterion-related validity for this measure is high; Knesevich et al. found a high correlation between the Hamilton score and a psychiatrist's global rating (r = 0.89), and between

the change in these ratings during treatment (r = 0.68) (Knesevich J 1977)[18]. Subscales, such as the HAM-$D_6$ which focuses on psychic anxiety and may be more sensitive to certain treatments, can be derived from the $HDRS_{17}$.

The original $HDRS_{17}$ scale lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the structured interview guide version of the $HDRS_{17}$ (the Structured Interview Guide for the Hamilton Depression Scale [SIGH-D]) will be used in the current study to facilitate and standardize gathering clinical information from the subject.

An example of the $HDRS_{17}$ is provided in Attachment 1.

*Clinical Global Impression Improvement (CGI-I)*

The clinical global impression – improvement (CGI-I) is a 7-point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

An example of the CGI-I is provided in Attachment 2.

**Patient Reported Outcome Assessments**

*Patient reported outcomes are included as a means of determining the frequency and severity of signs and symptoms of anxiety, depression, impairment in everyday life, and quality of life that can occur with or as a consequence of SAD and determine both their influence on treatment and their responsiveness to treatment. The anxiety, depression, sleep, and disability scales parallel the clinician administered scales and will therefore allow comparison of effects from the investigator and subject perspective.*

*Sheehan Disability Scale (SDS)*

The Sheehan Disability Scale (SDS) (Sheehan 1983)[22] is a composite of three self-rated items designed to measure the extent to which three major sectors in the patient's life are impaired by panic, anxiety, phobic, or depressive symptoms. This scale has been used widely in psychopharmacology randomized controlled trials and has been demonstrated to be sensitive to change, including a study of augmentation of treatment for refractory SAD (Pollack et al)[4]. This anchored visual analog scale uses visual-spatial, numeric, and verbal descriptive anchors simultaneously to assess disability across three domains: work, social life, and family life.

An example of the SDS is provided in Attachment 3.

*Generalized Anxiety Disorders (GAD-7)*

Generalized Anxiety Disorder 7 (GAD-7) is a self-reported questionnaire for screening and severity measuring of generalized anxiety disorder (GAD) and is of particular interest because of the frequent comorbidity of GAD with SAD. GAD-7 has seven items, which measure severity of various signs of generalized anxiety disorder according to reported response categories of "not at all," "several days," "more than half the days," and "nearly every day." Assessment is indicated by the total score, which made up by adding together the scores for the scale all seven items.

An example of the GAD-7 is provided in Attachment 4.

*Snaith-Hamilton Pleasure Scale (SHAPS)*

An instrument developed for the assessment of hedonic capacity is the 14-item, self-report, Snaith–Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) [23]. The SHAPS was developed to minimize cultural, gender, and age biases in the evaluation of hedonic capacity. It not only measures hedonic tone, but also its absence, i.e. anhedonia. Anhedonia can be a core symptom of depression. Four major domains are covered in the scale, namely interest/pastimes, social interaction, sensory experience, and food/drink.

An example of the SHAPS is provided in Attachment 7.

*Medical Outcomes Study Sleep-Revised (MOS Sleep-R)*

Symptoms of poor sleep commonly occur in anxiety and mood disorders. The Medical Outcomes Study Sleep-Revised (MOS Sleep-R) is a subject-completed scale containing 12 items that addresses various dimensions of sleep. The instrument yields six subscales: sleep disturbance, snoring, shortness of breath or headache, sleep adequacy, sleep somnolence, and sleep quantity. Most items are answered on 5-point Likert scales for 10 of the items, where 1="all of the time," and 5="none of the time," 1 item on sleep latency is answered on a 5 point Likert scale from 1="0-15 minutes" to 5="more than 60 minutes." The final item on the duration of sleep allows the subject to write in the number of hours slept per night. The version to be used in this study has a recall period of the 4 past weeks. Quantity of sleep is scored as the average number of hours slept per night. Other subscales scores are converted to a T-score with a mean of 50, standard deviation (SD) of 10 and range of 0 to 100, where higher scores indicate fewer sleep-related problems. The instrument has good data supporting its psychometric properties, and development history (Quick Start Guide for the MOS Sleep Scale-Revised 2010).

An example of the MOS Sleep-R is provided in Attachment 5.

*Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)*

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) rates 16 aspects of quality of life, including physical health, mood, activities of daily living and overall life satisfaction.

An example of the Q-LES-Q is provided in Attachment 8.

*Self-Assessment of Treatment Experience*

The Self-Assessment of Treatment Experience questionnaire is a 4-item self-report scale designed to provide additional information regarding the subject's subjective experience while taking the treatment.

An example of the Self-Assessment of Treatment Experience is provided in Attachment 9.

**Rationale for Biomarker Collection**

Biomarkers for PD activity (FAAH inhibition, as measured in plasma concentrations of FAAs) have been selected based on data from previous studies (42165279EDI1001 and 42165279EDI1002) in which those biomarkers showed dose-related changes.

**Rationale for DNA Collection**

It is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution and metabolism and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain inter-individual variability in the distribution and metabolism of a drug and may help to identify population subgroups that have different pharmacokinetic (PK) profiles of the drug.

A polymorphism in the FAAH gene (C385A) has been previously associated with reduced activity of the FAAH enzyme and levels of FAAH protein, potentially leading to increased AEA signaling in humans (Conzelman et al, 2012)[8]. Approximately one quarter of the population carries the associated A allele. Genotyping of this gene may help to explain variability in PD endpoints measured in this study. Additional pharmacogenomic analyses may be undertaken for the identification of other genetic factors that may influence PK, PD, safety, and/or tolerability of JNJ-42165279.

DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

## 3.3. Stopping Criteria

### 3.3.1. Individual Stopping Criteria[a]

In this phase 2a safety study, the following individual stopping rules will apply:

- The investigator or sponsor believes (e.g. that for safety or tolerability reasons such as a serious adverse event at least possibly related to the study drug) it is in the best interest of the subject to discontinue the study.
- The subject becomes pregnant

[a] This section has been amended per Amendment INT-1.

- A subject will be discontinued from the study when the QTc interval is higher than 500 msec. ECG events should be confirmed by repeat twice as soon as possible after the initial ECG, and the average value of the QTcB interval will be used to determine whether a subject should be discontinued. The subject will continue to be monitored by repeated 12-lead ECGs (at least every 60 min) until the ECG normalizes.
- Because of limited information on the effects of JNJ-42165279 on the human liver function a subject will be discontinued from the study if either of the following occur:
  - Aspartate transaminase (AST) and/or alanine transaminase (ALT) >3 x Upper Limit of Normal (ULN) (confirmed by repeat),
  - Total bilirubin >2 x ULN (confirmed by repeat).

### 3.3.2. Protocol Stopping Criteria

Medical monitoring by the sponsor will occur on a continual basis including laboratory and ECG data. A Data Review Committee (DRC) may be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study (see Section 11.8 Data Review Committee). The committee will meet periodically to review interim data. After the review, the DRC will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DRC charter.

## 4. SUBJECT POPULATION[a]

Approximately 137 subjects with SAD will be enrolled in the proof-of-concept study to ensure 53 subjects per treatment group completing the trial, assuming a dropout rate of approximately 15%. Because it is of the interest to assess in this study the effect of FAAH inhibition on symptoms of anxiety and depression, additional assessments with anxiety and depression scales will be included and subjects with co-morbid GAD and MDD will be allowed provided that SAD is judged by the investigator to be the primary indication for treatment. Other anxiety disorders and MDD are common comorbid conditions in subjects with SAD Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5). In a recent treatment study of refractory SAD, roughly a third of subjects had current/lifetime GAD, roughly a third had a lifetime history of MDD, and 10-15% (depending on the site) had a current episode of MDD (Pollock et al 2014)[4]. Subjects who have a current episode of MDD of sufficient severity that it should be the primary focus of treatment should be excluded. Any subject that is identified as having a current episode of MDD should be informed by the investigator and the potential risks and benefits of participating in the trial should be discussed with the subject before enrollment.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

[a] This section has been amended per Amendment INT-3.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

## 4.1. Inclusion Criteria[a]

Each potential subject must satisfy all of the following criteria to be enrolled in the study unless otherwise specified:

1. Subject must be a man or woman between 18 and 64 years of age, inclusive.

2. Subjects must have a primary DSM-5 diagnosis of SAD except those with performance only as a specifier. Subjects with a diagnosis of comorbid Generalized Anxiety Disorder (GAD) or Major Depressive Disorder (MDD) may be included if the investigator considers SAD to be the predominant diagnosis. Subjects with current or lifetime history of ADHD and specific phobia may be included as well.

3. Subjects must have a Liebowitz Social Anxiety Scale score ≥ 70 at screening and baseline.

4. Subjects with a current episode of MDD must have a $HDRS_{17}$ total score ≤ 18

5. Subjects must have a body mass index (BMI=weight/height²) between 18 and 35 $kg/m^2$, inclusive, at screening.

6. Criterion modified by Amendment 3.

   6.1. Before randomization, a **woman** must be either:

   - Not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 12 months, or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/L); permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy
   - Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly). This may include:
     - Established and ongoing use of oral hormonal methods of contraception in combination with barrier methods.
     - Established and ongoing use of patch, injected or implanted hormonal methods of contraception.
     - Placement of an IUD or IUS.

     Accepted barrier methods as indicated above include:

[a] This section has been amended per Amendments INT-1 and 3.

- condom with spermicidal foam/gel/film/cream/suppository
- occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

Note that a barrier method on its own is not sufficient.

- Male partner sterilization (the vasectomized partner should be the sole partner for that subject).
- True abstinence (when this is in line with the preferred and usual lifestyle of the subject).

Women must agree to continue using these methods of contraception throughout the study and for at least 3 months after receiving the last dose of study medication.

Note: If a woman of childbearing potential who is not heterosexually active becomes active after the start of the study, she must begin a highly effective method of birth control, as described above.

- **All women** must have a negative pregnancy test at screening and a negative urine pregnancy test on study day 1.
- **All women** must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after receiving the last dose of study drug.

7. Criterion modified by Amendment 3.

   7.1 **Men** who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control e.g., either condom or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners should also use an additional method of birth control (which may include a hormonal method, an intrauterine device [IUD] or an intrauterine system [IUS]) for at least the same duration.

8. Subjects must be otherwise healthy for their age group or medically stable with or without medication on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening or at baseline. If there are abnormalities, they must be consistent with the underlying illness in the study population and not a potential cause of cognitive impairment, with written concurrence with the sponsor's medical monitor.

9. Subjects must be otherwise healthy or medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel [including liver enzymes, other specific tests], hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the

abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.

10. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

11. Subject must be willing and able to fill out self-administered questionnaires.

12. Subject must be able to be compliant with self-administration of medication.

13. Subject must be able to swallow the study medication whole with aid of water.

14. Subject must sign 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.

## 4.2. Exclusion Criteria[a]

Any potential subject who meets any of the following criteria will be excluded from participating in the study unless otherwise specified:

1. Subjects who have performance only SAD are excluded. Subjects with other current significant psychiatric condition(s) (Axis 1 under DSM-IV), including, but not limited to, MDD with psychotic features (lifetime), bipolar disorder (including lifetime diagnosis), obsessive-compulsive disorder, borderline personality disorder, eating disorder (e.g., bulimia, anorexia nervosa), autism spectrum disorders, post-traumatic stress disorder (PTSD) or schizophrenia are excluded. Subjects with a diagnosis of comorbid GAD or MDD may be included.

2. Subject is currently receiving specific psychotherapy for SAD.

3. Has a history of more than two unsuccessful adequate pharmacological treatment trials for SAD, defined as lack of response to at least 10 weeks of treatment at adequate doses (e.g., paroxetine $\geq 40$ mg/day or its equivalent; or clonazepam $\geq 2.5$ mg/day or its equivalent).

4. Concurrent use of psychotropic medications. Benzodiazepine must be discontinued at least 7 days before screening and antidepressant therapy must be discontinued at least 2 weeks before screening (5 weeks for fluoxetine). Subjects who have had an adequate response to pharmacotherapy should not have this treatment discontinued solely for participation in the study. Subjects who have elected, in consultation with their health care provider, to discontinue pharmacotherapy because of difficulty tolerating the

[a] This section has been amended per Amendments INT-2 and 3.

medication may be eligible provided those treatments are stopped according to the guidelines above.

5. Subject has a history of or current thyroid disease, thyroid dysfunction and is currently untreated for it. Subjects treated for thyroid disease may be enrolled following review of their records of diagnosis and treatment history by the investigator and with written concurrence with the sponsor's medical monitor to ensure disease/treatment stability and compliance.

6. Criterion modified by Amendment 2.

   6.1. Subject has clinically significant abnormal findings on physical examination, neurological examination or clinically significant abnormal vital signs indicative of untreated illness (such as infection or hypertension).

7. Subject has a clinically significant abnormal finding on 12-lead ECG such as QTc >450 msec for males and females, Left Bundle Branch Block, AV Block second degree or higher, permanent pacemaker or implantable cardioverter defibrillator (ICD) at screening or baseline (Day 1 predose), or any finding which in the opinion of the investigator is not appropriate and reasonable for the population under study. ECG recordings and vital signs may be repeated once and for questions on findings on the ECG a local cardiologist should be consulted.

8. Subject has a history of or current liver or renal insufficiency; clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic disturbances (e.g. unstable situation needing monitoring or regular dose adaptations). Subjects with liver function analytes higher than the upper limit of normal at baseline should be reviewed with the sponsor. If the subject has any liver function tests >2 times the upper limit of normal, he/she should not be enrolled.

9. Subject has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with written concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

10. If a subject is using a drug with moderate/strong CYP3A4 inhibiting properties at, or prior to, Screening it must be discontinued at least within 1 month prior to Day 1. Note: an existing medication should not be stopped solely for the purpose of the subject entering the study. Moderate and strong inducers of CYP3A4 are prohibited during the study (See Attachment 13).

11. Subject has a history of positive tests for hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.

12. Subject tests positive for human immunodeficiency virus (HIV) or antibodies at Screening and is not being treated. Subjects with known HIV infection who are being treated, have shown a good response, are otherwise clinically stable, and can continue to comply with treatment may be enrolled. Subjects requiring treatment with medications that are moderate or strong CYP3A inhibitors (such as most protease inhibitors: see Attachment 13) must be excluded.

13. Subject has a history of drug or alcohol use disorder according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) criteria within 6 months before screening, or positive test result(s) for drugs of abuse (including barbiturates, opiates, cocaine, cannabinoids, amphetamines) at screening. A positive screen for benzodiazepines is allowed if related to recent treatment.

14. Subject has taken any disallowed therapies as noted in Section 8, Concomitant Therapy before the planned first dose of study drug.

15. Subject has known allergies, hypersensitivity, or intolerance to JNJ-42165279 or its excipients (refer to Investigator's Brochure).

16. Subject has received an investigational drug or used an investigational medical device within 3 months before the planned start of study or is currently enrolled in an investigational study.

17. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant or is a man who plans to father a child, while enrolled in this study or within 3 months after the last dose of study.

18. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19. Subject has had major surgery, (e.g. requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 4 weeks after the last dose of study drug administration.

    *Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate*.

20. Subject has a history of spontaneous, prolonged or severe bleeding.

21. Subject has donated one or more units (approximately 450 mL) of blood or had acute loss of an equivalent amount of blood within 90 days prior to study drug administration.

22. Subject has a current or recent history of clinically significant suicidal ideation within the past 6 months, corresponding to a score of 4 (active suicidal ideation with some

intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for ideation on the Columbia Suicide Severity Rating Scale (C-SSRS), or a history of suicidal behavior within the past year, as validated by the C-SSRS at screening or Day 1. Subjects with a prior suicide attempt, or prior serious suicidal ideation/plan ≥ 6 months ago, should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.

23. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

24. Subject is unable to comply with the study-specific requirements.

## 4.3. Prohibitions and Restrictions[a]

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. If a man that is sexually active with a woman of childbearing potential, he must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug.

2. Subjects must abstain from using illegal drugs (including cannabis and marihuana) from Screening through the end of the post-treatment phase. While cannabis and marihuana use may be sanctioned in some regions, use of cannabanoids during this trial would prevent detection of an effect of JNJ-42165279 and therefore must not be used while participating in the trial. If the subject has a positive urine drug screen during the study, he/she will be discontinued from the study.

3. Subjects are prohibited from taking/consuming grapefruit, grapefruit juice, Seville oranges or poppy seeds from Screening through the end of the post-treatment phase.

4. For a list of prohibited medications, please see Section 8 (Prestudy and Concomitant Therapy).

5. The use of limited amounts of alcohol (up to 2 drinks daily) will be allowed.

6. Subjects are not allowed to participate in cognitive behavioral therapy for SAD during their participation in the trial.

[a] This section has been amended per Amendment INT-1.

# 5. TREATMENT ALLOCATION AND BLINDING

## Treatment Allocation

### *Procedures for Randomization*

Central randomization will be implemented in this study. At the start of the double-blind phase, subjects will be randomly assigned to one of two treatment groups based on the first of two computer-generated randomization schedules prepared before the study by, or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks. Presence of comorbid MDD and country will be used as stratification factors.

### *Blinding*

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The investigator will not be provided with randomization codes. The codes will be maintained within the IVRS/IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (e.g., study medication plasma concentrations, plasma biomarkers) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IVRS/IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IVRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for required follow up evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

## 6. DOSAGE AND ADMINISTRATION[a]

Study medication will be provided as JNJ-42165279 tablets, strengths 25 mg and matching placebo, packaged in bottles. All tablets (JNJ-42165279 /placebo) are physically identical.

A study-site investigational product manual including instructions for dispensing, storage (on site and at home) and intake of the study medication will be supplied to the study-site.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. The sponsor may optionally develop tools to improve and/or document compliance to intake of study medication when locally feasible. This may include a diary or an electronic registration tool.

The selected 25 mg dose of JNJ-42165279 is expected to result in complete inhibition of FAAH enzyme in the brain throughout the dosing interval based on the outcome of the single ascending dose (42165279EDI1001), multiple ascending dose (42165279EDI1002) and PET occupancy (42165279EDI1003) studies.

During the treatment phase of this study dispensing and redispensing of their study medication will take place at the visits indicated in the Time and Events schedule. On Days of re-dispensing subjects will hand in their medication package dispensed previously and drug accountability will be performed.

Following last dosing, subjects will hand in their study medication received previously and final drug accountability will be performed.

During the entire blinded treatment period subjects will self-administer once-daily (q.d.) study drug (JNJ-42165279/placebo) with a glass of non-carbonated water, after completion of breakfast or a light snack, during the morning hours, according to the instructions provided by the investigator. During scheduled visits subjects will self-administer their study medication on site as described above which will be witnessed by designated study-site personnel at the study sites. On Day 1 study drug administration will be administered following completion of all predose assessments and will not be limited to the morning hours.

## 7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Study drug will be self-administered by subjects. As such the number of study drug dispensed will be recorded and compared with the number returned.

[a] This section has been amended as per Amendment INT-3.

At study visits, study drug will be self-administered on site, which will be witnessed by designated study-site personnel at the study sites.

Subjects will receive instructions on compliance with study drug administration upon study medication (bottle) dispensing. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject who is not compliant with taking the study drug.

## 8. PRESTUDY AND CONCOMITANT THERAPY[a]

Prestudy therapies administered up to 30 days before screening must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with signing of the initial informed consent until the end-of-study visit (Follow-up visit). Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening adverse events until resolution of the event.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Subjects are not allowed to participate in cognitive behavioral therapy for SAD while participating in this study. Investigators will inform subjects at their baseline visit and remind them at each subsequent visit of the need to enter socially feared situations in order to be able to determine how effective the medication is. At each visit (after the first visit), investigators will ask the subject about social situations that s/he has encountered since the last visit, and how s/he felt in those situations.

Prohibited Medications

Refer to Section 4.2 (Exclusion Criteria) for prohibited medications evaluated at Screening.

Subjects must agree not to use any of the following medications with psychotropic properties during study participation, including but not limited to:

- Psychiatric medications, including mood stabilizers, antipsychotics, antidepressants (e.g., MAOIs, SSRIs, SNRIs, or TCAs), or medications to treat anxiety (including benzodiazepines: see below)

[a] This section has been amended per Amendment INT-3.

- Sleep medications/medications to treat anxiety:
  - Benzodiazepines: Because concomitant use of benzodiazepines will confound the ability to interpret any potential anxiolytic efficacy signal, sleep aids and anxiolytics from the benzodiazepine class (e.g., lorazepam, temazepam, oxazepam, flurazepam, triazolam etc.) are prohibited from within 7 days prior to Screening and throughout the study duration.

    Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon and eszopiclone) are allowed on a PRN (as needed) basis during the study.
- Other Prohibited Medications include:
  - Sedating antihistamines
  - S-adenosyl methionine (SAMe), St. John's wort, ephedra or kava kava
  - Melatonin and ramelteon
  - Opiates, including morphine, codeine hydrocodone, oxycodone, and methadone
  - Anticonvulsants
  - Moderate and strong CYP3A4 inhibitors or inducers (Attachment 13)

# 9. STUDY EVALUATIONS

## 9.1. Study Procedures

### 9.1.1. Overview[a]

The Time and Events Schedule summarizes the visits as well as the frequency and timing of assessments applicable to this study. A visit window of +/- 3 calendar days will be allowed for all visits, unless otherwise indicated in the Time and Events Schedule. All visits are in principle single day visits however they may be performed over multiple days within the allowed visit window in case of logistical issues or subject's preference.

Information regarding collection, handling, shipment, and labeling of biological samples (including safety labs) will be provided in a separate lab manual.

Any changes to the lab manual will not result in a protocol amendment.

In the event of abnormal safety findings during the conduct of the study, additional measurements may be made immediately and subsequently at a frequency considered appropriate by the attending physician.

The time points for individual measures may be changed (with or without affecting the overall frequency of these investigations) prior to and during the study based on newly obtained data (e.g., interim analysis, DRC) to allow for optimal fit to the actual safety or PK/PD profile of the

[a] This section has been amended per Amendment INT-1.

study drug. This modification may result in a change in the overall frequency of the individual measures (e.g. safety measures, blood samplings) provided the maximal total blood volume collected per subject defined will not be exceeded. Such modifications, where performed only to allow optimal fit to the actual safety, PK/PD profile of the study drug, will not be considered to be an (substantial) amendment to the protocol.

Venous blood will be collected for all blood-based analysis. Actual dates and times of assessments will be recorded in the source documentation and CRF or lab requisition form. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Blood may be drawn by using a cannula or by venipuncture.

The exact times for each blood draw will be recorded in the CRF or lab requisition form. The order of multiple assessments within one protocol time point should also be the same throughout the study.

Vital signs will be recorded from the opposite arm from which the blood samples are being taken.

Blood pressures and ECGs should be recorded approximately 5 to 10 minutes before PK blood samples are taken.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The volume of blood collected per subject will be detailed in a separate lab manual.

For each subject, the maximum amount of blood drawn in this study will not exceed 200 mL.

### 9.1.2. Screening Phase[a]

Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, subjects will sign an informed consent form (ICF).

After giving initial written informed consent, subjects will be screened to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study.

Recording of adverse events/concomitant medication will start following consent and will continue until completion of the study.

During screening following assessments/procedures will be performed:

[a] This section has been amended per Amendments INT-2 and 3.

- Physical examination
- Neurological examination
- Body weight
- 12-lead ECG recording
- Body temperature
- Height
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- C-SSRS (baseline)
- Clinical safety laboratory assessments under fasted conditions, when feasible (including serology, hematology, serum chemistry, coagulation and urinalysis)
- Urine drug screen
- Alcohol screen (in blood)
- All women: Serum and urine pregnancy test
- Review of inclusion and exclusion criteria
- Complete/Review Medical History and Demographics
- Complete/Review Prestudy Therapy
- Review preplanned surgery/procedures
- Mini International Neuropsychiatric Interview (MINI)
- LSAS
- $HDRS_{17}$ using the SIGH-D
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

### 9.1.3. Double-Blind Treatment Phase[a]

**Day 1**

Subjects who successfully complete the screening examination will visit the clinical site on Day 1 during the morning hours.

Prior to dosing the following (baseline) assessments will be performed:

- Body weight
- 12-lead ECG recording (triplicate)

[a] This section has been amended per Amendments INT-1, 2 and 3.

- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- C-SSRS
- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- Blood sample collection for pharmacogenomics
- Blood sample collection for FAAs
- Urine drug screen
- Alcohol screen (in blood)
- All women: Urine pregnancy test
- Review of inclusion and exclusion criteria
- Randomization
- Dispense JNJ-42165279/placebo
- LSAS
- $HDRS_{17}$ using the SIGH-D
- SIGH-A
- SDS
- GAD-7
- SHAPS
- MOS Sleep-R
- Q-LES-Q
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

Study medication will be dispensed (incl. drug accountability) and administered as outlined in Section 6, Dosage and Administration. Subjects will self-administer their study medication q.d. as instructed.

On Day 1 dosing will not be time limited and will be performed following completion of the baseline (predose) assessments, which will be witnessed by designated study-site personnel at the study sites.

During the double-blind treatment period, following Day 1, subjects will return to the investigational site at regular time points as indicated in the Time and Events Schedule and further described below.

**Week 1 (Day 7)**

Subjects will visit the site at Day 7 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 7 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- C-SSRS
- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- WOCBP: urine pregnancy test.
- Drug accountability/Treatment compliance will be assessed.
- LSAS
- $HDRS_{17}$ using the SIGH-D
- SIGH-A
- CGI-I
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

**Week 2 (Day 14)**

Subjects will visit the site at Day 14 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 14 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- C-SSRS
- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- WOCBP: urine pregnancy test.
- Alcohol screen (in blood)
- Blood sample collection for PK of JNJ-42165279
- Drug accountability/Treatment compliance will be assessed.

- LSAS
- $HDRS_{17}$ using the SIGH-D
- SIGH-A
- CGI-I
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

**Week 4 (Day 28)**

Subjects will visit the site at Day 28 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 28 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Neurological examination
- Body weight
- 12-lead ECG recording
- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- C-SSRS
- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- WOCBP: urine pregnancy test.
- Blood sample collection for PK of JNJ-42165279
- Blood sample collection for FAAs
- Urine drug screen
- Alcohol screen (in blood)
- Dispense JNJ-42165279/placebo
- Drug accountability/Treatment compliance will be assessed.
- LSAS
- $HDRS_{17}$ using the SIGH-D
- SIGH-A
- CGI-I

- SDS
- GAD-7
- SHAPS
- MOS Sleep-R
- Q-LES-Q
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

**Week 6 (Day 42)**

Subjects will visit the site at Day 42 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 42 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- C-SSRS
- WOCBP: urine pregnancy test.
- Record adverse events and concomitant medication

**Week 8 (Day 56)**

Subjects will visit the site at Day 56 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 56 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Dispense JNJ-42165279/placebo
- Neurological examination
- C-SSRS
- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- WOCBP: urine pregnancy test.
- Alcohol screen (in blood)
- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)

- Drug accountability/Treatment compliance will be assessed.
- LSAS
- $HDRS_{17}$ using the SIGH-D
- SIGH-A
- CGI-I
- SDS
- GAD-7
- SHAPS
- MOS Sleep-R
- Q-LES-Q
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

**Week 10 (Day 70)**

Subjects will visit the site at Day 70 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 70 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- C-SSRS
- WOCBP: urine pregnancy test.
- Record adverse events and concomitant medication

**Week 12 (Day 84)**

Subjects will visit the site at Day 84 during morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration, which will be witnessed by designated study-site personnel at the study sites.

The following assessments will be performed at Day 84 as specified in the Time and Events schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Physical examination
- Neurological examination
- C-SSRS

- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)
- All women: Urine pregnancy test
- Urine drug screen
- Alcohol screen (in blood)
- Body temperature
- Body weight
- 12-lead ECG recording
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- Blood sample collection for FAAs
- Drug accountability/Treatment compliance will be assessed.
- LSAS
- $HDRS_{17}$ using the SIGH-D
- SIGH-A
- CGI-I
- SDS
- GAD-7
- SHAPS
- MOS Sleep-R
- Q-LES-Q
- Self-assessment of treatment experience
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

### 9.1.4. Posttreatment Phase (Follow Up)[a]

Minimally 7 and maximally 28 days following last dosing (Week 12), subjects will return to the clinical site for a safety follow up visit. The procedures to be completed during the follow up visit are listed in the Time and Events Schedule.

Investigators may re-contact the subject to obtain long-term follow-up information to determine the subject's safety or survival status (refer to Section 16.2.3, Informed Consent).

The following assessments will be performed at the follow-up visit as specified in the Time and Events schedule:

[a] This section has been amended per Amendments INT-3.

- Physical examination
- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis) – Only in case of any clinical significant abnormalities at Week 12
- All women: Blood and urine pregnancy test
- Alcohol screen (in blood)
- Body temperature
- Body weight
- 12-lead ECG recording (only in case of any clinical significant abnormalities at Week 12)
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- Behavioral guidance from the investigator
- Record adverse events and concomitant medication

## 9.2. Safety Evaluations

During the blinded treatment phase regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to: vital signs, ECG, physical examination, adverse events, safety labs, pregnancy tests, suicidality risks (C-SSRS).

The Data Review Committee (DRC) may decide to modify the frequency over time of specific safety assessments in case (newly obtained) data collected in this study would support this decision.

Details regarding the DRC are provided in Section 11.8.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

### 9.2.1. Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

### 9.2.2. Columbia Suicide Severity Rating Scale (C-SSRS)

Consistent with regulatory guidances, any occurrence of suicide-related thoughts and behaviors will be assessed. An interview to assess the risk of suicidal ideation and behavior will be conducted at the time points listed in the Time and Events Schedule.

The C-SSRS is a measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to

assess severity and track suicidal events through any treatment (Posner 2007)[19]. The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and suicidal behaviors. It can also be used during treatment to monitor for clinical worsening.

If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

See Attachment 10 and Attachment 11 for examples of the C-SSRS (baseline) and C-SSRS (since last visit), respectively.

### 9.2.3. Vital Signs

Vital signs (body temperature, pulse/heart rate, blood pressure) will be collected at the time points indicated in the Time and Events Schedule.

### 9.2.4. Electrocardiogram

Twelve-lead ECGs[2] will be collected at the time points listed in the Time and Events Schedule.

Only at Day 1 triplicate ECGs are required, i.e., 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

During the study, the clinical investigator will review the ECG for immediate management and to mark abnormalities. A description of the overall assessment (i.e., normal or abnormal plus reason) will be made and a copy of the trace will be placed with the source data.

### 9.2.5. Physical and Neurological Examinations[a]

The study investigator or other authorized and appropriately qualified designee will perform the physical examination.

Height will be measured at screening only. Body weight will be measured as per the Time and Events schedule.

The neurological examination can be adapted as necessary but should include mental status (orientation and memory); oculomotor motion and vision for cranial nerve testing; limb strength and abnormal movements for motor function; and tests of cerebellar function: gait, finger-to-nose, heel-to-shin, and rapid alternating movements. Tests of sensation (e.g., pain, vibration) should be included only if indicated by clinical history/symptoms.

[a] This section has been amended per Amendment INT-2.

The neurological examination will be done at screening, during the treatment phase and at the end of treatment visit (or early withdrawal visit) for all subjects. In addition neurological examinations will be completed when event driven. These events of interest include diplopia, vision impairment, gait disturbance and severe headache.

### 9.2.6. Clinical Laboratory Tests [a]

Blood samples (under fasted conditions whenever feasible) for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents. The following tests will be performed a central laboratory appointed by the Sponsor:

- Hematology Panel

-hemoglobin
-hematocrit
- red blood cell (RBC) count
- white blood cell (WBC) count with differential
- platelet count
- mean corpuscular volume
- mean corpuscular hemoglobin
- mean corpuscular hemoglobin concentration

- Coagulation

-prothrombin time
-activated partial thromboplastin time (aPPT)
- International normalized ratio (INR)

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-glucose
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-gamma-glutamyltransferase (GGT)
-total and direct bilirubin
-magnesium
-alkaline phosphatase
-creatine phosphokinase (CPK)
-lactic acid dehydrogenase (LDH)
-uric acid
-calcium
- phosphate
-albumin
-total protein
-cholesterol
-triglycerides
-high density lipid protein
-low density lipid protein

[a] This section has been amended per Amendment INT-3.

- Urinalysis

| Dipstick | Flow Cytometry |
|---|---|
| -specific gravity | -RBC |
| -pH | -WBS |
| -glucose | -epithelial cells |
| -protein | |
| -blood | |
| -ketones | Sediment |
| -bilirubin | -crystals |
| -urobilinogen | -casts |
| -nitrite | -bacteria |
| -leukocyte esterase | |

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. RBC, WBC, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

- Urine Drug Screen: opiates (including methadone), cocaine, amphetamines, cannabinoids, barbiturates, and benzodiazepines.
- Serology (hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV), HIV)
- Alcohol (blood) test

Pregnancy tests:

- In all women: serum β-HCG and urine pregnancy test will be performed at Screening and Follow-up and urine pregnancy test at study visits 2 and 9.
- In WOCBP: urine pregnancy test will be performed at all other timepoints.
- If the urine pregnancy test is positive, a serum β-HCG test will be performed.

The use of local laboratories is allowed in cases where initiation of treatment or safety follow-up is time-critical and the central laboratory results are not expected to be available before the need to begin dosing or if actions need to be taken for safety reasons (samples will be taken in parallel for the central laboratory).

## 9.3. Efficacy

### 9.3.1. Evaluations

*The nature and content of the primary and secondary clinician administered scales as well as the Patient Reported Outcome scales are described in section 3.2. Subscales derived from the principal scales are defined below.*

**Primary**

Liebowitz Social Anxiety Scale (LSAS)

The LSAS was designed to assess the range of social interaction and performance situations that individuals with social phobia may fear and/or avoid (Liebowitz, 1987)[3]. The 24 items in the scale are divided into two subscales that address social interactional (11 items) and performance (13 items) situations. The clinician asks the patient to rate fear and avoidance during the past week on 0–3 Likert-type scales; however, the clinician is given latitude to question the patient's responses and adjust the ratings accordingly. Thus, the LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction and avoidance of performance. An overall total score is often calculated by summing the total fear and total avoidance scores, and this index is the one most commonly employed in studies of the pharmacotherapy of social phobia (R. G. Heimberg, K. J. Horner, H. R. Juster, S. A. Safren, E. J. Brown, F. R. Schneier, M. R. Liebowitz. Psychometric properties of the Liebowitz Social Anxiety Scale. Psychological Medicine, 1999, 29, 199–212)[17].

**Secondary**

- Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A)

The total and subscale scores for the SIGH-A and $HDRS_{17}$ will be used to evaluation of efficacy on symptoms of anxiety and depression.

- $HAM\text{-}A_6$

The $HAM\text{-}A_6$ is a 6-item subscale derived from the original Hamilton Anxiety scale (HAM-A) (Hamilton 1959[13]; Hamilton 1969[15]). Because the HAM-A, like the Hamilton Depression Rating Scale ($HDRS_{17}$), is a multi-dimensional scale, Bech derived a 6-item subscale, the $HAM\text{-}A_6$, comprising five psychic anxiety symptoms: anxious mood, psychic tension, fears, intellectual disturbances, and anxious behavior observed at the interview, as well as one somatic item, muscular tension (Bech 2007)[10], with a score range of 0 to 24. In an analysis of four pooled dose-response trials in GAD, a Mokken analysis of the $HAM\text{-}A_6$ yielded Loevinger coefficients above 0.40 individually and combined, indicating that unlike the full HAM-A, the $HAM\text{-}A_6$ subscale is uni-dimensional. Given a fundamental requirement for a drug to be considered to have an anxiolytic effect is that it has shown efficacy in terms of symptom reduction in the core symptoms of anxiety, and as these symptoms are captured by $HAM\text{-}A_6$ (which is more in accordance with the DSM-5 criteria for GAD than the full HAM-A), the total $HAM\text{-}A_6$ score is considered a sufficient statistic.

- Hamilton Depression Rating Scale ($HDRS_{17}$)

A 6-item subscale from the $HDRS_{17}$ ($HAM\text{-}D_6$) will be analyzed as it has been shown to be a uni-dimensional scale that provides information to core depressive symptoms and is sensitive to treatment response (Bech 1975)[9].

In addition the anxiety-somatization factor total score from the $HDRS_{17}$ will be included (Cleary 1977)[11]. A cut-off of ≥ 7 on this factor has been used to define subjects with anxious depression in prior clinical trials (Fava 2008)[12].

- Clinical Global Impression Improvement (CGI-I)

**Patient Reported Outcome Assessments**

- Sheehan Disability Scale (SDS)
- Generalized Anxiety Disorders (GAD-7)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- MOS Sleep-R
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
- Self-Assessment of Treatment Experience

### 9.3.2. Endpoints

**Primary**
The primary efficacy endpoint for this study will be the improvement in social anxiety symptoms, as measured by the change from baseline in the LSAS total score from baseline to the 12-week endpoint in the double-blind treatment phase.

The primary comparison will be between the JNJ-42165279 and the placebo treatment groups.

**Secondary**
Secondary efficacy endpoints will include:

- The change from baseline to the 12-week endpoint for LSAS Fear/Anxiety and Avoidance subscales.
- The distribution (number and percentage) of subjects who are responders (≥50% improvement from baseline) and remitters (≥30% improvement from baseline) on the LSAS total score at the 12-week endpoint.
- The change from baseline to the 12-week endpoint for: SIGH-A total score, $HAM\text{-}A_6$ score, $HDRS_{17}$ total score, $HDRS_{17}$ anxiety/somatization factor total score, $HAM\text{-}D_6$ score and the (CGI-I) value.
- The distribution (number and percentage) of subjects who are responders (≥50% improvement from baseline) on SIGH-A total score assessed at the 12-week endpoint.

**Exploratory**

- The change from baseline to the 12-week endpoint for: SDS (Sheehan Disability Scale) GAD-7, Snaith-Hamilton Pleasure Scale (SHAPS) and MOS Sleep-R.
- The change from baseline to the 12-week endpoint for Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
- Self-Assessment of Treatment Experience scale
- The change from baseline to the 12-week endpoint for: $HDRS_{17}$ total score, $HDRS_{17}$ anxiety/somatization factor total score and $HAM\text{-}D_6$ score in subjects with comorbid MDD.
- The change from baseline to the 12-week endpoint for: SIGH-A total score and $HAM\text{-}A_6$ score in subjects with comorbid GAD.
- The distribution (number and percentage) of subjects with comorbid MDD who are responders on depressive symptoms (based on two definitions: either ≥50% or ≥30% improvement on $HDRS_{17}$ total score from baseline) at the 12-week endpoint.
- The distribution (number and percentage) of subjects with comorbid GAD who are responders on anxious symptoms (≥50% improvement on SIGH-A total score from baseline) at the 12-week endpoint.

## 9.4. Biomarkers

During the study, the following PD evaluations will be performed at the time points indicated in the Time and Events schedule: plasma concentrations of FAAs (AEA, PEA and OEA). Venous blood samples may be stored and used for future analysis of JNJ-42165279 metabolites and exploratory proteomics and metabolomics or other markers related to neuropsychiatric disorders.

## 9.5. Pharmacokinetics

### 9.5.1. Evaluations

Venous blood samples for analysis of JNJ-42165279 in plasma will be collected at the time-points indicated in the Time and Events Schedule.

Blood samples will be used to evaluate the plasma pharmacokinetics of JNJ-42165279. Samples collected for analyses of JNJ-42165279 plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

### 9.5.2. Analytical Procedures

**Pharmacokinetics**

Plasma will be analyzed to determine concentrations of JNJ-42165279 using a validated, specific, and sensitive LC-MS/MS method by or under the supervision of the sponsor.

Concentration time data will allow estimation of individual PK parameters for JNJ-42165279 using a population PK modeling approach. It will also help to understand potential differences

between healthy subjects and subjects with SAD. Time and days of JNJ-42165279 plasma concentration assessment were chosen to gather maximal information about the PK properties of JNJ-42165279 while minimizing subject burden regarding blood sampling.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma samples may be stored for future analysis of protein binding and the metabolite profile.

### 9.5.3. Pharmacokinetic Parameters

PK analyses of the plasma concentrations will be undertaken to estimate peak plasma concentration and systemic exposure of JNJ-42165279. Based on the individual plasma concentration-time data, if sufficient data are available, the following PK parameters of JNJ-42165279 will be estimated at steady state in subjects receiving a dose of JNJ-42165279 using population PK modeling:

$C_{max}$ maximum plasma concentration

$t_{max}$ time to reach the maximum plasma concentration

$AUC_{\tau}$ area under the plasma concentration-time curve from 0 to $\tau$ hours post dosing (time $\tau$ is the dosing interval)

The parameters of interest for the statistical analysis will be the log-transformed estimated dose normalized AUC and $C_{max}$. All ratios will be calculated as differences of least square means of the appropriate model on the log-scale, and will be presented after back-transformation to the original sale with the corresponding 90% confidence intervals (CIs).

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-42165279 will be derived using population PK modelling. Baseline covariates (e.g., body weight, age, sex, CrCL, race) may be included in the model, if relevant.

## 9.6. Pharmacogenomic Evaluations

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence PK, PD, safety, and/or tolerability of JNJ-42165279 and to enable the development of safer, more effective and ultimately individualized therapies in the future. DNA samples will be analyzed for the FAAH gene.[7] Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to JNJ-42165279. They may also be used to develop tests/assays related to JNJ-42165279. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to JNJ-42165279 clinical endpoints. Analyses may be performed across multiple clinical studies.

### 9.7. Sample Collection and Handling

PK and PD (biomarker) sampling/assessment times and sampling volumes can be adapted without protocol amendment provided that the maximal volume collected per subject specified per protocol will not be exceeded.

Refer to the Time and Events schedule for the timing and frequency of all sample collections.

The exact dates and times of blood sampling must be recorded in the CRF or lab requisition form.

Instructions for the collection, handling, storage, and shipment of samples will be provided in a separate lab manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the lab manual.

All the assays and instruments used in this study will be performed by trained operators at the Sponsor or designated laboratories in Europe or the US on coded samples.

Venous blood samples may be stored and used for future analysis of JNJ-42165279 metabolites and exploratory proteomics and metabolomics or other markers related to neuropsychiatric disorders.

## 10. SUBJECT COMPLETION/WITHDRAWAL

### 10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 12 (Day 84) of the double-blind phase. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

### 10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject to discontinue study treatment

- A subject experiences a severe or serious adverse event while receiving treatment, that is considered at least possibly related to study drug
- Noncompliance with study drug (i.e. less than 80% compliance) during the blinded treatment phase

If a subject discontinues study treatment before the end of the blinded phase the subject will be asked to complete the End-Of-Treatment Visit (Week 12 assessments) if not obtained earlier and the Follow-up visit as per Time and Events Schedule.

## 10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- It is not possible to obtain blood
- Serious violation of protocol procedures
- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

Any subject who withdraws after receiving the study drug will be asked, if not yet obtained, to have the Week 12 assessment performed. In addition the subjects should have a follow-up evaluation as described in Section 9.1.4.

**Withdrawal from the Use of Samples in Future Research**

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

# 11. STATISTICAL METHODS

Statistical analyses will be conducted by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the safety, tolerability, pharmacodynamic and pharmacokinetic data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

## 11.1. Subject Information

For all subjects who receive at least one dose of study drug descriptive statistics will be provided.

## 11.2. Sample Size Determination[a]

The sample size for the study is based on the assumption of a treatment difference of at least 10 points in the mean change from baseline to the endpoint in LSAS total score between JNJ-42165279 treatment group and placebo. A standard deviation of 24 in the change in LSAS total score from baseline is used based on published data. [4,5,6] To detect the treatment difference of 10 points (which is judged to be clinically relevant [4,5,6]) with a power of 90% at an overall 1-sided significance level of 0.20, 53 subjects in each group are required. When adjusted for a drop-out rate of approximately 15% of subjects, the required number of subjects is 61 per treatment group. To replace 15 subjects who prematurely stopped the study when the study was put on hold, the total number of subjects entering the study will be increased from 122 to137.

The impact of this sample size (N=137) on the JNJ– 42165279 effect size to be detected for the other continuous secondary and exploratory endpoints for different values of significance level and power, assuming a drop-out rate of 15%, are presented in Table 1.

**Table 1: JNJ–42165279 effect size to be detected for different values of significance level and power, assuming a drop-out rate of 15%**

| 1-sided significance level | Power | Effect size to be detected |
|---|---|---|
| 0.10 | 80% | 0.4 |
| 0.10 | 90% | 0.5 |
| 0.20 | 80% | 0.3 |
| 0.20 | 90% | 0.4 |

## 11.3. Efficacy Analysis

All efficacy analyses will be based on the intention-to-treat (ITT) analysis set. The JNJ-42165279 treatment group will be compared with placebo using the primary efficacy endpoint- change from baseline in total LSAS score during the double-blind treatment phase.

The comparison will be performed by means of a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, JNJ-42165279) and time-by-treatment interaction as factors and baseline total LSAS score as a continuous covariate and a country and presence of comorbid MDD as categorical covariates. Other covariates of interest may be included in the MMRM model. An unstructured variance-covariance matrix will be used. The treatment-placebo differences will be obtained using the appropriate contrast in the MMRM models at the 12-week endpoint.

The change from baseline for the secondary continuous efficacy endpoints will be analyzed in the same way as for the LSAS total score.

Sensitivity analyses of the primary endpoint will be performed using ANCOVA model; these will be detailed further in the Statistical Analysis Plan.

[a] This section has been amended per Amendment INT-3.

Descriptive statistics for values and changes from baseline (where applicable) will be provided by treatment group for all efficacy measures, including subscale scores for selected scales, at each time point of the double-blind treatment phase.

Frequency tables for remission and response of social anxiety symptoms (derived from LSAS), as well as frequency tables for response of depressive and anxiety symptoms (derived from the $HDRS_{17}$ and SIGH-A) will be provided by treatment group at each time point of the double-blind treatment phase.

## 11.4. Safety Analysis[a]

All subjects receiving at least one dose of study drug will be included in the safety analysis. All safety analyses will be performed based on the safety analysis set, which will include all randomized subjects who receive at least 1 dose of study drug.

### Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the double-blind treatment phase (i.e., treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least one occurrence of the given event will be summarized by treatment group. Summaries will be provided for all subjects receiving at least one dose of study drug in this study, and will include adverse events from this study.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who withdraw due to an adverse event, or who experience a severe or a serious adverse event.

### Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point, and for changes from baseline.

The number and percentage of subjects experiencing a laboratory result below or above normal reference ranges will be provided for each laboratory analyte by treatment group. Summaries will be provided for all subjects receiving at least one dose of study drug in this study.

A listing of subjects with any laboratory result outside the reference ranges will be provided.

[a] This section has been amended per Amendment INT-2.

**12-Lead ECG**

Heart rate and ECG intervals (RR, PR, QRS and QT) as well as corrected QT intervals according to Bazett's formula (QTcB) and Fridericia's formula (QTcF) from the 12-lead ECG will be summarized at baseline and at each scheduled time point and for changes from baseline using descriptive statistics.

The number and percentage of subjects with at least one occurrence of a treatment-emergent potentially clinically important QTc measurement (QTc value >450, >480, or >500 msec) or with a change from baseline in QTc>30 msec will be summarized by treatment group. Summaries will be provided for all subjects receiving at least one dose of study drug in this study.

Data listings of subjects with any potentially clinically important values (QTc value >450, >480, or >500 msec) or with a change from baseline in QTc >30 msec will be provided.

**Vital Signs**

Descriptive statistics of pulse, blood pressure (systolic and diastolic) (supine and standing), temperature and body weight values and changes from baseline will be summarized at each scheduled time point.

**Physical and Neurological Examinations**

The number and percentage of subjects with a change from normal at baseline to abnormal at any post-baseline exam will be tabulated by treatment group.

Subjects with abnormal findings will be presented in a data listing.

**Columbia Suicide Severity Rating Scale (C-SSRS)**

Results from the C-SSRS will be tabulated by treatment group for all subjects receiving at least one dose of study drug in this study.

## 11.5. Interim Analysis

An interim analysis for purpose of sample size re-estimation may be performed after 50% of the subjects are recruited if observed SD substantially deviates from the hypothesized or if the drop-out rate substantially deviates from the assumed. If one is required, details will be included in the statistical analysis plan.

## 11.6. Pharmacodynamic Analysis

Where appropriate, the relationship between plasma concentrations of JNJ-42165279 and corresponding biomarkers (plasma concentrations of FAAs [AEA, PEA, and OEA]) will be plotted to evaluate the relationships graphically. If deemed appropriate, suitable PK/PD population models will be applied to describe the exposure-effect relationships.

## 11.7. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis

Population PK modeling of plasma concentrations of JNJ-42165279 will be undertaken. In view of the sparse sampling foreseen for this study, data may be combined with a selection of Phase 1 data (e.g. from studies 42165279EDI1001, 42165279EDI1002, and/or 42165279EDI1004) in order to support a relevant structural model.

Population PK/PD analysis of biomarkers and/or efficacy markers may also be performed, and a suitable dose- and/or exposure-response model may be developed. If necessary or relevant for the analysis, Phase 1 data may be integrated to inform the model structure or key parameter values.

## 11.8. Data Review Committee (DRC)

Based on the safety signal observed in six clinical studies in healthy subjects exposed to JNJ-42165279 to date, a DRC will be set up if any relevant additional safety findings are observed.

To protect the integrity of the clinical study, the DRC members (medical and statistical experts, internal or external to J&J) will not be study team personnel or otherwise directly involved in the study conduct, data management, or statistical analysis for the study.

The objectives and scope of the DRC and the operational and logistical procedures to perform the DRC activities will be documented in the DRC charter prior to the review of any data by the DRC.

Only blinded information, conclusions, or recommendations will be communicated by the DRC chairperson while the study is ongoing.

# 12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

## 12.1. Definitions

### 12.1.1. Adverse Event Definitions and Classifications

**Adverse Event**

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not

related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

**Serious Adverse Event**

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

**Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-42165279, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.[1]

**Adverse Event Associated With the Use of the Drug**

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

### 12.1.2. Attribution Definitions

**Not Related**

An adverse event that is not related to the use of the drug.

**Doubtful**

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

**Possible**

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

**Probable**

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

**Very Likely**

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

### 12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

**Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** Sufficient discomfort is present to cause interference with normal activity.

**Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g., laboratory abnormalities).

## 12.2. Special Reporting Situations[a]

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion)

For this study safety events of interest include diplopia, vision impairment, gait disturbance and severe headache. These events will trigger a neurological examination and a narrative of the event.

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

## 12.3. Procedures

### 12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All other events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 12.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

[a] This section has been amended per Amendment INT-2.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

### 12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for (part of) the duration of the treatment period.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

### 12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

## 12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

# 13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

### 13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

### 13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

## 14. STUDY DRUG INFORMATION

### 14.1. Physical Description of Study Drug(s)

The JNJ-42165279 solid dosage formulation will be supplied as 25-mg tablets.

The JNJ-42165279 placebo will be supplied as film-coated tablets, matching visually to the active tablets. JNJ-42165279/placebo will be manufactured and provided under the responsibility of the sponsor.

Refer to the Investigator's Brochure[1] for a list of excipients.

### 14.2. Packaging

The study drug will be packaged in individual subject kits. Each kit will consist of 1 bottle containing 31 tablets.

All JNJ-42165279/placebo solid formulation study drug will be dispensed in child-resistant packaging.

### 14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

### 14.4. Preparation, Handling, and Storage

All study medication will be stored in a secure area with restricted access.

The JNJ-42165279 and placebo solid dosage formulation must be stored at controlled room temperatures ranging from 15°C to 30°C, as indicated on the product specific labeling.

Additional guidance and detailed instructions for the clinical site dosing procedures and storage conditions are described in the Dose Preparation Instructions/ Pharmacy manual or equivalent document.

Refer to the Dose Preparation Instructions/Pharmacy Manual for additional guidance on study drug dispensing, dosing process, and handling.

### 14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

## 15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with, but not limited to, the following supplies:

- Investigator Brochure for JNJ-42165279
- Pharmacy manual/study site investigational product manual
- Laboratory manual
- IVRS/IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF

# 16. ETHICAL ASPECTS

## 16.1. Study-Specific Design Considerations[a]

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The study treatment duration in this study of subjects with SAD is supported by the available toxicology and clinical data (see Investigator's Brochure)[1]. A safety signal of reversible mild elevation of liver transaminases was identified in the Phase 1 multiple dose study, occurring in subjects exposed to more than 4 days dosing with 100 mg. To mitigate the risk to subjects participating in this trial, a dose of 25 mg was selected that should allow for testing of the pharmacology of the compound, all subjects will be screened and those with evidence of pre-existing liver dysfunction will not be enrolled, clinical safety labs will be collected every 2 weeks and available for ongoing monitoring by the investigator and sponsor, 'stopping rules' have been developed for stopping treatment in the event that subjects have greater than 3 fold increase in transaminases or have an increase in total bilirubin to >2 x ULN, and a Data Review Committee may be established to monitor the study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study if the frequency of discontinuations exceeds 10% of subjects or increases of 5 fold over the ULN are observed.

A placebo arm is warranted and necessary to allow for an accurate assessment of the safety and tolerability of the study drug. Treatment with placebo dosing is not equivalent to non-treatment. All medication treatment will occur within the context of carefully supervised and supportive care. Only investigators experienced in the treatment of SAD will participate in the trial and can provide expert guidance on the alternatives for treatment if subjects elect to discontinue the study prior to the last visit or after the completion of the study. MDD, both lifetime and current episode are known comorbidities in subjects with SAD. Subjects experiencing a current episode of MDD severe enough to warrant treatment of depression as the primary focus will be excluded and advised as to resources available for treatment.

Only experienced and qualified physicians are allowed to perform the applicable procedures.

The total blood volume to be collected will not exceed 200 mL, which is considered to be safe and acceptable in comparison to a Red Cross blood donation.

[a] This section has been amended per Amendment INT-1.

## 16.2. Regulatory Ethics Compliance

### 16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

### 16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC about the study completion [(if applicable, the notification will be submitted through the head of investigational institution)].

### 16.2.3. Informed Consent

Each subject (or a legally acceptable representative, if applicable) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects (or their legally acceptable representatives, if applicable) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that

their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject (or legally acceptable representative, if applicable), is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject (or legally acceptable representative, if applicable), will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's (or his or her legally acceptable representative's) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

### 16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative, if applicable) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and

confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

### 16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-42165279, to understand SAD, to understand differential drug responders, and to develop tests/assays related to JNJ-42165279 and SAD. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

### 16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

## 17. ADMINISTRATIVE REQUIREMENTS

### 17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

## 17.2. Regulatory Documentation

### 17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

### 17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

## 17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

## 17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (e.g., physical examination, laboratory assessment) and documented in the source documents.

## 17.5. Case Report Form Completion

CRFs are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the

study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (e.g., pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

## 17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory and ECG data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

## 17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

## 17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

## 17.9. Study Completion/Termination

### 17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

### 17.9.2. Study Termination

The sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

## 17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

## 17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-42165279 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-42165279, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the

information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

**Registration of Clinical Studies and Disclosure of Results**

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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# ATTACHMENTS

## Attachment 1: 17-Item Hamilton Depression Rating Scale (HDRS17)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

**1 DEPRESSED MOOD** (sadness, hopeless, helpless, worthless)
- 0 [ ] Absent.
- 1 [ ] These feeling states indicated only on questioning.
- 2 [ ] These feeling states spontaneously reported verbally.
- 3 [ ] Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
- 4 [ ] Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

**2 FEELINGS OF GUILT**
- 0 [ ] Absent.
- 1 [ ] Self reproach, feels he/she has let people down.
- 2 [ ] Ideas of guilt or rumination over past errors or sinful deeds.
- 3 [ ] Present illness is a punishment. Delusions of guilt.
- 4 [ ] Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

**3 SUICIDE**
- 0 [ ] Absent.
- 1 [ ] Feels life is not worth living.
- 2 [ ] Wishes he/she were dead or any thoughts of possible death to self.
- 3 [ ] Ideas or gestures of suicide.
- 4 [ ] Attempts at suicide (any serious attempt rate 4).

**4 INSOMNIA: EARLY IN THE NIGHT**
- 0 [ ] No difficulty falling asleep.
- 1 [ ] Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
- 2 [ ] Complains of nightly difficulty falling asleep.

**5 INSOMNIA: MIDDLE OF THE NIGHT**
- 0 [ ] No difficulty.
- 1 [ ] Patient complains of being restless and disturbed during the night.
- 2 [ ] Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

**6 INSOMNIA: EARLY HOURS OF THE MORNING**
- 0 [ ] No difficulty.
- 1 [ ] Waking in early hours of the morning but goes back to sleep.
- 2 [ ] Unable to fall asleep again if he/she gets out of bed.

**7 WORK AND ACTIVITIES**
- 0 [ ] No difficulty.
- 1 [ ] Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
- 2 [ ] Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
- 3 [ ] Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
- 4 [ ] Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

**8 RETARDATION** (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
- 0 [ ] Normal speech and thought.
- 1 [ ] Slight retardation during the interview.
- 2 [ ] Obvious retardation during the interview.
- 3 [ ] Interview difficult.
- 4 [ ] Complete stupor.

**9 AGITATION**
- 0 [ ] None.
- 1 [ ] Fidgetiness.
- 2 [ ] Playing with hands, hair, etc.
- 3 [ ] Moving about, can't sit still.
- 4 [ ] Hand wringing, nail biting, hair-pulling, biting of lips.

**10 ANXIETY PSYCHIC**
- 0 [ ] No difficulty.
- 1 [ ] Subjective tension and irritability.
- 2 [ ] Worrying about minor matters.
- 3 [ ] Apprehensive attitude apparent in face or speech.
- 4 [ ] Fears expressed without questioning.

**11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:**
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating
- 0 [ ] Absent.
- 1 [ ] Mild.
- 2 [ ] Moderate.
- 3 [ ] Severe.
- 4 [ ] Incapacitating.

**12 SOMATIC SYMPTOMS GASTRO-INTESTINAL**
- 0 [ ] None.
- 1 [ ] Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
- 2 [ ] Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

**13 GENERAL SOMATIC SYMPTOMS**
- 0 [ ] None.
- 1 [ ] Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
- 2 [ ] Any clear-cut symptom rates 2.

**14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)**
- 0 [ ] Absent.
- 1 [ ] Mild.
- 2 [ ] Severe.

**15 HYPOCHONDRIASIS**
- 0 [ ] Not present.
- 1 [ ] Self-absorption (bodily).
- 2 [ ] Preoccupation with health.
- 3 [ ] Frequent complaints, requests for help, etc.
- 4 [ ] Hypochondriacal delusions.

**16 LOSS OF WEIGHT** (*RATE EITHER a OR b*)

| a) According to the patient: | b) According to weekly measurements: |
|---|---|
| 0 [ ] No weight loss. | 0 [ ] Less than 1 lb weight loss in week. |
| 1 [ ] Probable weight loss associated with present illness. | 1 [ ] Greater than 1 lb weight loss in week. |
| 2 [ ] Definite (according to patient) weight loss. | 2 [ ] Greater than 2 lb weight loss in week. |
| 3 [ ] Not assessed. | 3 [ ] Not assessed. |

**17 INSIGHT**
- 0 [ ] Acknowledges being depressed and ill.
- 1 [ ] Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- 2 [ ] Denies being ill at all.

Total score: [ ][ ]

This scale is in the public domain.

**Attachment 2: Clinical Global Impression – Improvement (CGI-I)**

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment. Compared to his/her condition at admission to the project, how much has the patient changed?

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**Attachment 3: Sheehan Disability Scale (SDS)**

## Sheehan Disability Scale

**A brief, patient rated, measure of disability and impairment.**

Please mark ONE circle for each scale.

**WORK* / SCHOOL**

**The symptoms have disrupted your work / school work:**


☐ I have not worked / studied at all during the past week for reasons unrelated to the disorder.
* Work includes paid, unpaid volunteer work or training

**SOCIAL LIFE**

**The symptoms have disrupted your social life / leisure activities:**


**FAMILY LIFE / HOME RESPONSIBILITIES**

**The symptoms have disrupted your family life / home responsibilities:**


**Days Lost**

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

**Days Unproductive**

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

**Attachment 4: Generalized Anxiety Disorders (GAD-7)**

## GAD-7

| Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)* | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Feeling nervous, anxious or on edge | 0 | 1 | 2 | 3 |
| 2. Not being able to stop or control worrying | 0 | 1 | 2 | 3 |
| 3. Worrying too much about different things | 0 | 1 | 2 | 3 |
| 4. Trouble relaxing | 0 | 1 | 2 | 3 |
| 5. Being so restless that it is hard to sit still | 0 | 1 | 2 | 3 |
| 6. Becoming easily annoyed or irritable | 0 | 1 | 2 | 3 |
| 7. Feeling afraid as if something awful might happen | 0 | 1 | 2 | 3 |

*(For office coding: Total Score T____ = ____ + ____ + ____ )*

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

**Attachment 5: Medical Outcomes Study (MOS) - 12-Item Sleep Scale Acute - Revised**

# Your Sleep

**For each of the following questions, please mark an ☒ in the one box that best describes your answer.**

**1. How long did it usually take for you to fall asleep during the past 4 weeks?**

| 0-15 minutes | 16-30 minutes | 31-45 minutes | 46-60 minutes | More than 60 minutes |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**2. On the average, how many hours did you sleep each night during the past 4 weeks?**

Write in number of hours per night: ☐☐

**3. How often during the past 4 weeks did you...**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b get enough sleep to feel rested upon waking in the morning? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c awaken short of breath or with a headache? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d feel drowsy or sleepy during the day? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| e have trouble falling asleep? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**How often during the past 4 weeks did you...**

| | | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| f | awaken during your sleep time and have trouble falling asleep again? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| g | have trouble staying awake during the day? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| h | snore during your sleep? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| i | take naps (5 minutes or longer) during the day? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| j | get the amount of sleep you needed? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**Attachment 6: Liebowitz Social Anxiety Scale (LSAS)**

| Pt Name: | | Pt ID #: |
|---|---|---|
| Date: | Clinic #: | Assessment point: |

Fear or Anxiety:
0 = None
1 = Mild
2 = Moderate
3 = Severe

Avoidance:
0 = Never (0%)
1 = Occasionally (1—33%)
2 = Often (33—67%)
3 = Usually (67—100%)

| | Fear or Anxiety | Avoidance | |
|---|---|---|---|
| 1. Telephoning in public. (P) | | | 1. |
| 2. Participating in small groups. (P) | | | 2. |
| 3. Eating in public places. (P) | | | 3. |
| 4. Drinking with others in public places. (P) | | | 4. |
| 5. Talking to people in authority. (S) | | | 5. |
| 6. Acting, performing or giving a talk in front of an audience. (P) | | | 6. |
| 7. Going to a party. (S) | | | 7. |
| 8. Working while being observed. (P) | | | 8. |
| 9. Writing while being observed. (P) | | | 9. |
| 10. Calling someone you don't know very well. (S) | | | 10. |
| 11. Talking with people you don't know very well. (S) | | | 11. |
| 12. Meeting strangers. (S) | | | 12. |
| 13. Urinating in a public bathroom. (P) | | | 13. |
| 14. Entering a room when others are already seated. (P) | | | 14. |
| 15. Being the center of attention. (S) | | | 15. |
| 16. Speaking up at a meeting. (P) | | | 16. |
| 17. Taking a test. (P) | | | 17. |
| 18. Expressing a disagreement or disapproval to people you don't know very well. (S) | | | 18. |
| 19. Looking at people you don't know very well in the eyes. (S) | | | 19. |
| 20. Giving a report to a group. (P) | | | 20. |
| 21. Trying to pick up someone. (P) | | | 21. |
| 22. Returning goods to a store. (S) | | | 22. |
| 23. Giving a party. (S) | | | 23. |
| 24. Resisting a high pressure salesperson. (S) | | | 24. |

**Attachment 7: Snaith-Hamilton Pleasure Scale (SHAPS)**

This questionnaire is designed to measure your ability to experience pleasure *in the last few days*. It is important to read each statement very *carefully*.

Tick *one* of the boxes ☐ to indicate how much you agree or disagree with each statement.

1. **I would enjoy my favourite television or radio programme**
   - Strongly disagree ..... ☐
   - Disagree..... ☐
   - Agree..... ☐
   - Strongly agree ..... ☐
2. **I would enjoy being with my family or close friends**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐
3. **I would find pleasure in my hobbies and pastimes**
   - Strongly disagree ..... ☐
   - Disagree..... ☐
   - Agree..... ☐
   - Strongly agree ..... ☐
4. **I would be able to enjoy my favourite meal**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐
5. **I would enjoy a warm bath or refreshing shower**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐
6. **I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread**
   - Strongly disagree ..... ☐
   - Disagree..... ☐
   - Agree..... ☐
   - Strongly agree ..... ☐
7. **I would enjoy seeing other people's smiling faces**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐

8. **I would enjoy looking smart when I have made an effort with my appearance**

Strongly disagree ..... ☐

Disagree..... ☐

Agree..... ☐

Strongly agree ..... ☐

9. **I would enjoy reading a book, magazine or newspaper**

Definitely agree..... ☐

Agree..... ☐

Disagree..... ☐

Strongly disagree ..... ☐

10. **I would enjoy a cup of tea or coffee or my favourite drink**

Strongly disagree ..... ☐

Disagree..... ☐

Agree..... ☐

Strongly agree ..... ☐

11. **I would find pleasure in small things e.g. a bright sunny day, a telephone call from a friend**

Strongly disagree ..... ☐

Disagree..... ☐

Agree..... ☐

Strongly agree ..... ☐

12. **I would be able to enjoy a beautiful landscape or view**

Definitely agree..... ☐

Agree..... ☐

Disagree..... ☐

Strongly disagree ..... ☐

13. **I would get pleasure from helping others**

Strongly disagree ..... ☐

Disagree..... ☐

Agree..... ☐

Strongly agree ..... ☐

14. **I would feel pleasure when I receive praise from other people**

Definitely agree..... ☐

Agree..... ☐

Disagree..... ☐

Strongly disagree ..... ☐

Reproduced from: Snaith et al. (1995) A scale for the assessment of hedonic tone. The Snaith-Hamilton Pleasure Scale. *British Journal of Psychiatry*, **167**, 99-103.

**Attachment 8: Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)**

Name:_____ Date:_____

**Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)**

Taking everything into consideration, during the past week how satisfied have you been with your.....

| | Very Poor | Poor | Fair | Good | Very Good |
|---|---|---|---|---|---|
| .....physical health? | 1 | 2 | 3 | 4 | 5 |
| .....mood? | 1 | 2 | 3 | 4 | 5 |
| .....work? | 1 | 2 | 3 | 4 | 5 |
| .....household activities? | 1 | 2 | 3 | 4 | 5 |
| .....social relationships? | 1 | 2 | 3 | 4 | 5 |
| .....family relationships? | 1 | 2 | 3 | 4 | 5 |
| .....leisure time activities? | 1 | 2 | 3 | 4 | 5 |
| .....ability to function in daily life? | 1 | 2 | 3 | 4 | 5 |
| .....sexual drive, interest and/or performance?* | 1 | 2 | 3 | 4 | 5 |
| .....economic status? | 1 | 2 | 3 | 4 | 5 |
| .....living/housing situation?* | 1 | 2 | 3 | 4 | 5 |
| .....ability to get around physically without feeling dizzy or unsteady or falling?* | 1 | 2 | 3 | 4 | 5 |
| .....your vision in terms of ability to do work or hobbies?* | 1 | 2 | 3 | 4 | 5 |
| .....overall sense of well being? | 1 | 2 | 3 | 4 | 5 |
| .....medication? (If not taking any, check here _____ and leave item blank.) | 1 | 2 | 3 | 4 | 5 |
| .....How would you rate your overall life satisfaction and contentment during the past week? | 1 | 2 | 3 | 4 | 5 |

*If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.

**Attachment 9: Self-Assessment of Treatment Experience**

These questions are about your overall experience while on the study medication. Please answer each question by selecting the response that best describes you.

1. **Considering all aspects of your depression, since starting this study medication, overall would you say your depression is:**

   **(Select one response)**

   ☐ Very much improved

   ☐ Much improved

   ☐ Improved (just enough to make a difference)

   ☐ No change

   ☐ Worse (just enough to make a difference)

   ☐ Much worse

   ☐ Very much worse

2. **Please select your response to the following statements.**

| | **Yes** | **No** |
|---|---|---|
| **While taking the study medication:** | | |
| I felt more relaxed | ☐ | ☐ |
| My mood improved | ☐ | ☐ |
| I was better able to perform my daily activities | ☐ | ☐ |
| I felt more interested in social activities | ☐ | ☐ |
| My sleep improved | ☐ | ☐ |
| I felt less distracted | ☐ | ☐ |

**3. During the past week (7 days), how would you rate your appetite (your overall desire to eat)?**

**(Select one response)**

- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

**4. How interested would you be in continuing to take the study medication if needed?**

**(Select one response)**

- ☐ Not at all interested
- ☐ A little interested
- ☐ Moderately interested
- ☐ Very interested
- ☐ Extremely interested

**Attachment 10: Columbia Suicide Severity Rating Scale – BASELINE**

| *SUICIDAL IDEATION* | |
|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | Lifetime: Time He/She Felt Most Suicidal |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>*Have you wished you were dead or wished you could go to sleep and not wake up?*<br>If yes, describe: | Yes ☐ No ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.<br>*Have you actually had any thoughts of killing yourself?*<br>If yes, describe: | Yes ☐ No ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it….and I would never go through with it".*<br>*Have you been thinking about how you might do this?*<br>If yes, describe: | Yes ☐ No ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*<br>*Have you had these thoughts and had some intention of acting on them?*<br>If yes, describe: | Yes ☐ No ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>*Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*<br>If yes, describe: | Yes ☐ No ☐ |
| *INTENSITY OF IDEATION* | |
| *The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe ). Ask about time he/she was feeling the most suicidal.*<br>*Most Severe Ideation:* ____ _____<br>*Type # (1-5)* *Description of Ideation* | Most Severe |
| **Frequency**<br>*How many times have you had these thoughts?*<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ___ |
| **Duration**<br>*When you have the thoughts, how long do they last?*<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ___ |
| **Controllability**<br>*Could /can you stop thinking about killing yourself or wanting to die if you want to?*<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ___ |
| **Deterrents**<br>*Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply; wish to die only | ___ |
| **Reasons for Ideation**<br>*What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*<br>(1) Completely to get attention, revenge or a reaction from others.<br>(2) Mostly to get attention, revenge or a reaction from others.<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). | ___ |

Version 7/19/08

| *SUICIDAL BEHAVIOR*<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | Lifetime |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>*Have you made a suicide attempt?*<br>*Have you done anything to harm yourself?*<br>*Have you done anything dangerous where you could have died?*<br>*What did you do?*<br>*Did you_____ as a way to end your life?*<br>*Did you want to die (even a little) when you_____?*<br>*Were you trying to end your life when you _____?*<br>*Or did you think it was possible you could have died from_____?*<br>*Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent)<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.<br>Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>*Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>*Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note).<br>*Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*<br>If yes, describe: | Yes ☐ No ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ |

| *Answer for Actual Attempts Only* | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g. surface scratches).<br>1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |

## Attachment 11: Columbia Suicide Severity Rating Scale – Since Last Visit

| *SUICIDAL IDEATION* | |
|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | Since Last Visit |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>*Have you wished you were dead or wished you could go to sleep and not wake up?*<br>If yes, describe: | Yes ☐ No ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>*Have you actually had any thoughts of killing yourself?*<br>If yes, describe: | Yes ☐ No ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*<br>*Have you been thinking about how you might do this?*<br>If yes, describe: | Yes ☐ No ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*<br>*Have you had these thoughts and had some intention of acting on them?*<br>If yes, describe: | Yes ☐ No ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>*Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*<br>If yes, describe: | Yes ☐ No ☐ |
| ***INTENSITY OF IDEATION*** | |
| *The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe ).*<br>*Most Severe Ideation:* ____ _____<br>*Type # (1-5)* *Description of Ideation* | Most Severe |
| **Frequency**<br>*How many times have you had these thoughts?*<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ___ |
| **Duration**<br>*When you have the thoughts, how long do they last?*<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ___ |
| **Controllability**<br>*Could /can you stop thinking about killing yourself or wanting to die if you want to?*<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ___ |
| **Deterrents**<br>*Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply; wish to die only | ___ |
| **Reasons for Ideation**<br>*What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*<br>(1) Completely to get attention, revenge or a reaction from others.<br>(2) Mostly to get attention, revenge or a reaction from others.<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). | ___ |

Version 7/19/08

| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | Since Last Visit |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>*Have you made a suicide attempt?*<br>*Have you done anything to harm yourself?*<br>*Have you done anything dangerous where you could have died?*<br>*What did you do?*<br>*Did you_____ as a way to end your life?*<br>*Did you want to die (even a little) when you_____?*<br>*Were you trying to end your life when you _____?*<br>*Or did you think it was possible you could have died from_____?*<br>*Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent)<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>*Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>*Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one' s death by suicide (e.g. giving things away, writing a suicide note).<br>*Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*<br>If yes, describe: | Yes ☐ No ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ |
| **Completed Suicide:** | Yes ☐ No ☐ |
| ***Answer for Actual Attempts Only*** | Most Lethal Attempt Date: |
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g. surface scratches).<br>1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ |

**Attachment 12: Anticipated Events**

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events based on reports by healthy subjects in Phase 1 studies:

- headache
- dizziness
- fatigue
- increase of hepatic enzymes

**Reporting of Anticipated Events**

These events will be captured on the eCRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events.

Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

**Attachment 13: Prohibited Cytochrome P450 Inhibitors and Inducers**

| Inducers | Inhibitors |
|---|---|
| Carbamazepine | Amprenavir |
| Dexamethasone | Atazanavir |
| Efavirenz | Clarithromycin |
| Ethosuximide | Clotrimazole |
| Isoniazid | Darunavir |
| Nevirapine | Delavirdine |
| Phenobarbital | Diltiazem |
| Phenytoin | Elvitegravir/Cobicistat |
| Prednisone | Erythromycin |
| Rifabutin/rifampicin | Fluconazole |
| St. John's Wort | Fluoxetine |
| | Fluvoxamine |
| | Fosamprenavir |
| | Grapefruit |
| | Indinavir |
| | Itraconazole |
| | Ketoconazole |
| | Lopinavir |
| | Metronidazole |
| | Mibefradil |
| | Miconazole |
| | Nefazodone |
| | Nelfinavir |
| | Nifedipine |
| | Norfloxacin |
| | Omeprazole |
| | Propoxyphene |
| | Quinine |
| | Ritonavir |
| | Saquinavir |
| | Seville oranges |
| | Simeprevir |
| | Tipranavir |
| | Troleandomycin |
| | Verapamil |
| | Zafirlukast |

## INVESTIGATOR AGREEMENT

JNJ-42165279
Amendment INT-3 42165279SAX2001

### INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Dr. Mark Schmidt

Institution: Janssen Research & Development, a division of Janssen Pharmaceutica NV

Signature PPD Date: 28 Aug 2017
(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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## LAST PAGE