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 Major Depressive Disorder with Anxious Distress.

Protocol 42165279MDD2001; Phase 2a

Amendment INT-5

JNJ-42165279

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

EudraCT NUMBER: 2015-002007-29

Status: Approved
Date: 24 October 2017
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica N.V.
EDMS number: EDMS-ERI-104283605, 7.0

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	12 Jun 2015
Amendment INT-1	31 Aug 2015
Amendment INT-2	03 July 2017
Amendment INT-3	13 July 2017
Amendment INT-4	25 August 2017
Amendment INT-5	24 October 2017

Amendments below are listed beginning with the most recent amendment.

Amendment INT-5 (24 October 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:

- On regulator's request, subjects with abnormal high liver function analytes will not be allowed in the study.
- An exclusion criterion for breast feeding women was missing.
- On request of investigators: Venlafaxine (immediate release) added to the list of allowed antidepressant drugs.
- On request of investigators: added instructions on the use of PRN non-benzodiazepine sleep aids.
- Added: more specific instructions of the calculation of QTc interval to determine stopping or exclusion criteria.

Applicable Section(s)	Description of Change(s)
Section 3.3.1 Individual stopping criteria	Changed: QTc interval is higher than 500 msec Into QTc interval (QTcF; QTcB if ECG machine only shows QTcB) is higher than 500 msec
Section 4.2 Exclusion criteria	Exclusion criterion 9 Changed: …such as QTc >450 msec… Into …such as QTcF (QTcB if ECG machine only shows QTcB) >450 msec… Exclusion criterion 10 Changed: 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 screening need to be reviewed with the sponsor for acceptability prior to enrollment.~~ into 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 renal or liver function analytes significantly**

	higher (more than 1.5 times the upper limit of normal) at screening are not eligible for the study.
	Exclusion criterion 19 Changed: ~~Subject is a man who plans to conceive a child, while enrolled in this study or within 3 months after the last dose of study~~. into **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**.
Section 8, Prestudy and concomitant medication	Added to list of allowed antidepressant medication: venlafaxine. Changed: Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon and eszopiclone) are allowed on a PRN (as needed) basis during the study. into Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon and eszopiclone) are allowed on a PRN (as needed) basis during the study, however, not more than 2 nights in a row and not more than a total of 3 nights weekly during the double-blind treatment period.

Amendment INT-4 (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:

- 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.
- Add the optional use of a diary or electronic device to document the intake of study medication.

Applicable Section(s)	Description of Change(s)
Synopsis	Safety Evaluations Added: In all women, serum and urine pregnancy test will be performed at Screening and at Visit 10. 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. Added: Footnote t: 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. Changed: footnote k. Performed for all women. Serum and urine pregnancy test ~~performed at Screening, urine pregnancy test at 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.

Section 3.2. Population

Added:
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 and each study visit during the double-blind phase. 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."

Removed: (of non-child bearing potential)

Section 4.1 Inclusion criteria

Inclusion criteria 6 and 7 will be replaced by:

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:
    - 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 9.1.3	Added: urine pregnancy test at visits 2 to 9 for WOCBP and serum pregnancy test at Visit 10 for all women.
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 at study visit 10. • In WOCBP: serum β-HCG and 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.

Rationale: Add the optional use of a diary or electronic device to document the intake of study medication.

Synopsis and Section 6	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.

Amendment INT-3 (13 July 2017)

This amendment is considered to be non-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:

- Correction of wordings and inconsistencies.

Applicable Section(s)	Description of Change(s)
4.1	Inclusion criterion 6: Replaced “Menstrual” by “Childbearing age”
Time & Events schedule	Footnote b: replace “7 to 28 days” into “7 to 21 days”

Amendment INT-2 (03 July 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
- Adaptation of the number of subjects participating in the study. This will be changed from 140 to 143 to replace 3 subjects who had to stop early when the study was put on hold.
- To add neurological examinations to confirm the safety of participation in the trial and treatment with JNJ-42165279.
- Change in allowed medication and control of drug intake.

Applicable Section(s)	Description of Change(s)
Rationale: To update the information on toxicology	
Section 1.1	Text on CCI [redacted] and CCI [redacted] added to reflect recent non-clinical study results.

Applicable Section(s)	Description of Change(s)
Rationale: Adaptation of the number of subjects participating in the study. This will be changed from 140 to 143 to replace 3 subjects who had to stop early when the study was put on hold	
Synopsis and Sections 3.1 and 4.0	Changed 140 subjects participating in this study into 143 subjects.
Synopsis and Section 11.1	Added sentence: To replace 3 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 approximately 140 to 143.
Rationale: • Better clarify that administration of study medication at the site needs to be witnessed by study site personnel. • Add melatonine and ramelteon as prohibited medication.	
Section 6	Added in last paragraph: ..which will be witnessed by designated study-site personnel at the study sites.
Section 9.1.3	Replaced: Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration. by: 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	Replace Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon, eszopiclone and ramelteon) are allowed on a PRN (as needed) basis during the study. With Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon and eszopiclone) are allowed on a PRN (as needed) basis during the study. Added to list of "Other prohibited medication": - melatonine and ramelteon.

Applicable Section(s)	Description of Change(s)
Rationale: 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 and 3.1 Overview of Study Design Synopsis	Screening Screening will include obtaining informed consent, assessment of study inclusion and exclusion criteria, medical history, physical examination, **neurological examination** and safety evaluations. Safety Evaluations: 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) - Footnote "s" added: A neurological examination will also be completed in case of adverse event of interest.
4.2 Exclusion criteria	Exclusion criteria 8 has been updated as follows: 8.1 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).
9.1.2 Screening Phase 9.1.3 Double-Blind Treatment Phase	Neurological examination added Neurological examination added at Week 5, Week 9 and Week 11 visits
9.2.5 Physical **and Neurologica**l Examinations	Title updated and text added: 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.
11.3 Safety Analysis 12.2 Special Reporting Situations	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.

Applicable Section(s)	Description of Change(s)
	Sub title updated as follows: Physical **and Neurological** Examinations. Text added: 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 (31 Aug 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 clarify the updated procedure performed by an independent central rater and to address FDA comments.

Applicable Section(s)	Description of Change(s)
Rationale: Updated procedure performed by an independent central rater at screening	
Synopsis – Overview of Study Design – Time & Events schedule. 3.1. Overview of Study Design 3.2. Study Design Rationale 9.1.2. Screening	Description of the updated procedure performed by an independent central rater at screening
Rationale: Clarification of the duration of the ongoing SSRI/SNRI antidepressant treatment and clarification of the procedures performed by an independent central rater at screening	
Synopsis – Overview of Study Design Synopsis – Overview of Study Design	Maximal duration of "no longer than 14 weeks" with their current antidepressant has been deleted to allow more flexibility.
4.1. Inclusion Criteria.	Inclusion criteria 2, 3 and 4 updated

Rationale: Addition of vilazodone to the list of the allowed antidepressants as requested by FDA	
Synopsis – Overview of Study Design – 3.1. Overview of Study Design 8. Prestudy and Concomitant Therapy	Vilazodone added to the list of the allowed antidepressants
Rationale: Clarification of exclusion criteria # 19	
4.2. Exclusion criteria	"father a child" replaced by "conceive a child"
Rationale: Administrative: correction content of Attachment 6 : Perceived Stress Scale (PSS)	
Attachment 6	CPFQ questionnaire deleted

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 Major Depressive Disorder with Anxious Distress.

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 CC mg and a multiple dose regimen of 100 mg once-daily (q.d.) 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. A phase 2a study in patients with social anxiety disorders (SAD) is ongoing.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the efficacy in terms of reduction of symptoms of depression and anxiety, as assessed by the change from baseline on a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$), and overall safety and tolerability of treatment with adjunctive JNJ-42165279 compared to placebo in subjects with major depressive disorder (MDD) with anxiety symptoms who have had inadequate response to treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonergic/noradrenergic reuptake inhibitor (SNRI).

Secondary Objectives

The secondary objectives of this study are:

- To assess the efficacy of JNJ-42165279 on core symptoms of anxiety ($HAM\text{-}A_6$).
- To assess the efficacy of JNJ-42165279 using dimensional analyses of both anxiety and depression ($HDRS_{17}$ and SIGH-A).
- To assess the efficacy of JNJ-42165279 on the response and remission of depressive and anxiety symptoms (derived from $HDRS_{17}$ and SIGH-A).
- To assess the plasma pharmacokinetic (PK) profile of JNJ-42165279 administered as once daily (*qd)* in male and female subjects with MDD with anxious distress using a population PK approach and explore its relationship with efficacy and safety parameters.

[a] This section has been amended per Amendments INT-1, 2 and 4.

Exploratory Objectives

The exploratory objectives are:

- To evaluate the impact of treatment with adjunctive JNJ-42165279 compared to placebo on Clinical Global Impression (CGI) and exploratory clinician-rated and patient-reported assessments (CUDOS-A, CPFQ, SHAPS, MOS Sleep-R, PSS and Self-Assessment of Treatment Experience).
- To explore for differential efficacy in subjects with melancholic features and subjects with comorbid anxiety disorders, as reported on the Mini International Neuropsychiatric Interview (MINI) diagnostic interview and patient-reported assessments.
- To explore CCI [redacted] (including but not limited to CCI [redacted] and CCI [redacted] that may be related to clinical response, nonresponse, or safety and tolerability parameters of JNJ-42165279.
- To explore the relationship between plasma PK and plasma concentrations of FAAs (anandamide [AEA], palmitoylethanolamide [PEA] and oleoylethanolamide [OEA]) in subjects with MDD with anxious distress.

Hypothesis

The primary hypothesis is that 6-weeks of treatment with adjunctive JNJ-42165279 is superior to placebo in improving symptoms of depression and anxiety, as measured by the change from baseline in the $HDRS_{17}$, in subjects with MDD with anxiety symptoms who have had an inadequate response to an SSRI/SNRI.

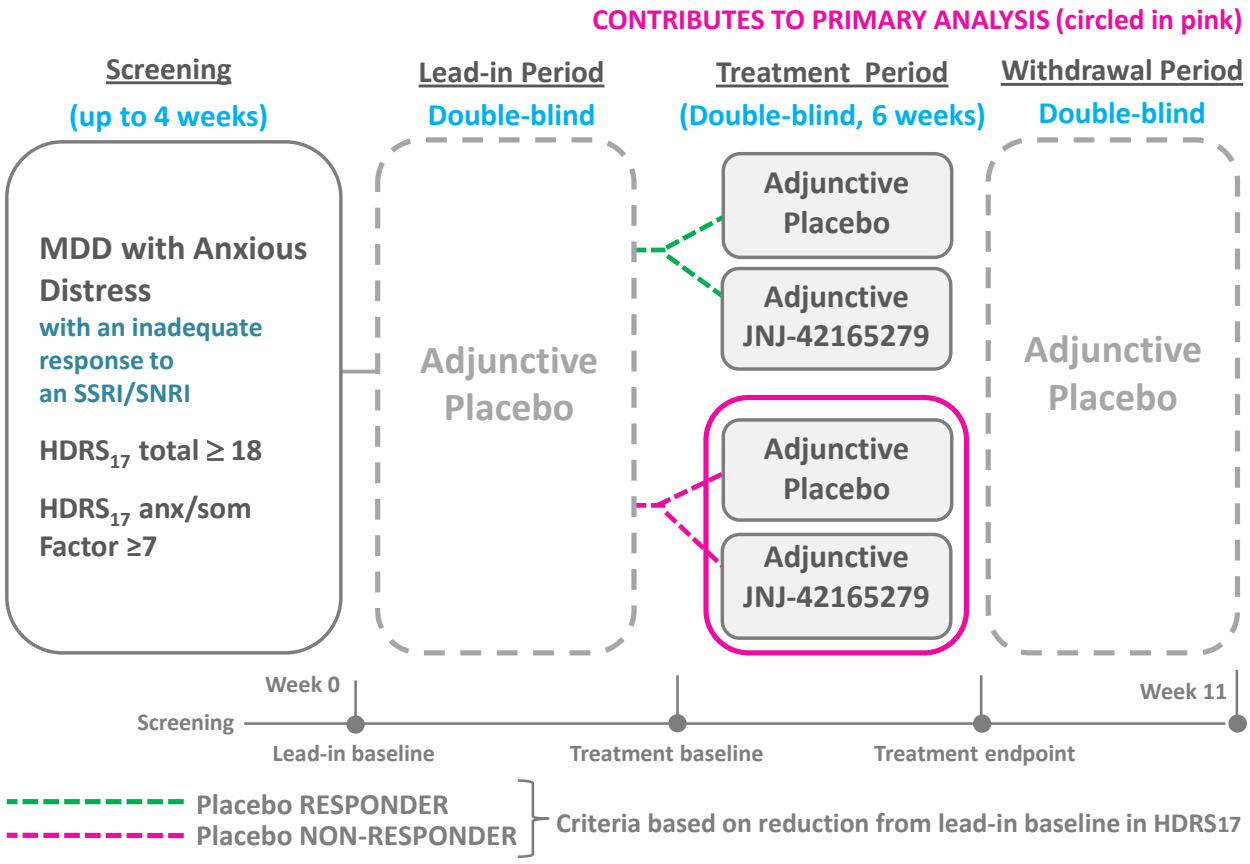
OVERVIEW OF STUDY DESIGN

This is a multi-center, double-blind, placebo-controlled, randomized, parallel-group study in subjects with MDD with anxious distress who have had inadequate response to SSRI/SNRI treatment. Subjects with MDD with anxious distress who have had treatment initiated with an SSRI/SNRI will be evaluated at the investigation site. Site assessments will be reviewed and verified by an independent central rater. The review by a central rater will include the clinical history of MDD, SSRI/SNRI treatment of adequate dose and duration for the current episode of depression, and current symptom severity on the $HDRS_{17}$. Assessments by qualified site personnel including the MINI, ATRQ, and $HDRS_{17}$ will be recorded for review and validation of the suitability of the subject for enrollment into the study by an independent central rater contracted by the sponsor. Subjects who meet the inclusion and exclusion criteria and are enrolled will be maintained on the SSRI/SNRI treatment throughout the study to determine whether adjunctive treatment can reduce symptoms of MDD with anxious distress. For each subject, the study will consist of three phases: a screening phase of up to 4 weeks, double-blind treatment phase lasting up to 11 weeks, and a 3-week post-treatment (follow up) phase. The double-blind treatment phase of the trial will consist of 3 periods. The first period is a placebo lead-in of double-blind duration, after which subjects will enter the treatment period when they will be randomly assigned to JNJ-42165279 or continuation on placebo for 6 weeks. Subjects who successfully complete the treatment period prior to the end of Week 11, will be treated with placebo for the remaining time of the double-blind phase of the study, which will vary depending on the duration of the placebo lead-in for the specific subject. The total study duration for each subject will be approximately 18 weeks. The end of study is defined as the date of the last visit of the last patient undergoing the trial. Investigators and subjects will remain blinded to the exact duration of the subject lead-in and withdrawal period during the entire study duration.

Approximately 143 subjects will enter the double-blind placebo lead-in period. At the end of the lead-in period, response status of the subjects will be assessed according to the double-blind response criteria based on reduction in $HDRS_{17}$ relative to lead-in baseline. Both, lead-in placebo responders and lead-in placebo non-responders will be randomly assigned in a 1:1 ratio to either 25 mg of JNJ-42165279 or placebo in the treatment period. The primary efficacy analyses will be based on the treatment period data from the lead-in non-responders (94 subjects).

The study will be an outpatient study.

Subject-Specific Trial Scheme



Screening

After giving written informed consent, subjects may be screened over a period of up to 4 weeks to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study.

A critical element of the screening is determination that subjects must have (1) reached a pre-defined optimal dose based on the Antidepressant Treatment Response Questionnaire –ATRQ (Chandler 2010), (2) received treatment at the optimal dose for at least 6 weeks with their current antidepressant and (3) failed to respond to the current antidepressant therapy. The following antidepressants are permitted: citalopram, escitalopram, sertraline, paroxetine, venlafaxine XR, desvenlafaxine, duloxetine, milnacipram, vilazodone, and vortioxetine. Subjects will continue to take their SSRI/SNRI treatment at an adequate and tolerated dose (i.e. monotherapy) throughout the study provided it is one of the

antidepressants allowed by this protocol. No antidepressant dose changes are permitted from Screening through the end of the study, including the post-treatment phase. Subjects participating in this study must also fulfill the criteria for current/past/recurrent major depressive illness as per MINI). Furthermore, subjects with a primary psychiatric diagnosis other than MDD will be excluded (as per the MINI).

For inclusion, subjects must have a $HDRS_{17}$ total score ≥18 and a $HDRS_{17}$ anxiety/somatization factor score ≥7 while having been treated with one of the antidepressants approved in this protocol at an adequate dose and for at least 6 continuous weeks. The clinical history of the current episode of MDD will be assessed by the MINI and supplementary subject validation questions; the lack of response to antidepressant therapy symptom severity will be assessed by the $HDRS_{17}$, and the antidepressant treatment history based on the subject's report during the screening interview by the ATRQ. Each of these assessments will be conducted by qualified personnel at the site at screening and will be recorded to allow independent validation of the suitability of the subject for enrollment by an independent central rater contracted by the sponsor.

Screening will include obtaining informed consent, assessment of study inclusion and exclusion criteria, medical history, physical examination, neurological examination and safety evaluations.

The screening visit may be split into 2 visits.

Adverse events will be collected starting after the informed consent form (ICF) has been signed until the final study procedure at the final visit.

Subjects who are deemed eligible for randomization will enter the double blind treatment phase.

Double Blind Treatment Phase

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

Lead-in period

Subjects who successfully complete the screening will visit the clinical site/unit on Day 1 and will be treated with placebo for the entire duration of the lead-in period. Investigators and subjects will be blinded to exact duration of each subject-specific lead-in period throughout the study.

Treatment period

At the end of the lead-in period both: placebo lead-in responders and placebo lead-in non-responders will be randomized to receive either adjunctive placebo or JNJ-42165279 in a 1:1 ratio for a 6-weeks treatment period. Investigators and subjects will remain blinded to exact timing of the randomization and study drug treatment assignment for each subject.

Withdrawal period

Subjects who successfully complete the treatment period prior to the end of Week 11 will enter withdrawal period where they will be treated with placebo for the remaining time of the double-blind phase of the study, which will vary depending on the duration of the placebo lead-in for a given subject. Investigators and subjects will be blinded to exact duration of each subject-specific withdrawal period.

During the double-blind 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 (PD) effects will be explored at the time points listed in the Time and Events Schedule (TES).

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 21 days following last dosing (Week 11), 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 subjects and female subjects who are not able to bear children with MDD with anxious distress who are between 18 and 64 years of age inclusive, with screening and baseline symptom severity as measured by the total score $HDRS_{17}$ ≥18 and a $HDRS_{17}$ anxiety/somatization factor score ≥7.

Approximately 143 subjects with MDD with anxious distress will be enrolled in this proof-of-concept study.

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 (MAD) (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 at Visit 10. 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 MDD. 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

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

The $HDRS_{17}$ is included as a means to determine the frequency and severity of signs and symptoms of depression and determine both their influence on treatment and their responsiveness to treatment.

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 and determine both their influence on treatment and their responsiveness to treatment.

- HAM-A6 (derived from SIGH-A)
- HDRS17 anxiety/somatization factor (derived from $HDRS_{17}$)
- HAM-D_6 subscale (derived from $HDRS_{17}$)
- 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 the population included in this study, the impact of treatment on sleep symptoms, and impairment in daily life.

- Clinically Useful Depression Outcome Scale (with anxious distress specifier) (CUDOS-A)
- Cognitive and Physical Functioning Questionnaire (CPFQ)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Medical Outcomes Study Sleep-Revised (MOS Sleep-R)
- Perceived Stress Scale (PSS)
- Self-Assessment of Treatment Experience

BIOMARKER AND PHARMACOGENOMIC (DNA) 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).

Biomarker samples (blood, saliva) will be collected for the assessment of CCI (including but not limited to CCI related to CCI to allow for CCI and for an CCI evaluation. Saliva samples will be collected for the measurement of CCI concentrations.

A pharmacogenomic blood sample will be collected to assess whether the subject is carrier of the CCI and to identify CCI and/or CCI factors that may influence the CCI of JNJ-42165279.

DNA and biomarker samples may be used to help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug. DNA and Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

STATISTICAL METHODS

Sample Size Determination

The sample size for the study is determined based on the assumption of a minimally relevant treatment effect size of 0.45 in the mean change from baseline to the endpoint in $HDRS_{17}$ total score between JNJ-42165279 treatment group and placebo. The assumed effect size is based on review of the literature looking at the treatments for MDD and MDD with anxious distress (Lee 2004 and McIntyre 2007) taking into account that the effect size in enriched population is expected to be higher. A standard deviation (SD) of 7.5 in the change in $HDRS_{17}$ total score from baseline is estimated based on a previously conducted clinical trial in similar patient population (40411813DAX2001) allowing for a higher variability.

The effect size of 0.45 (under SD assumption of 7.5) translates to a treatment difference between JNJ-42165279 and placebo at endpoint of 3.5 points. Detection of this magnitude of effect size with a power of 90% at an overall 1-sided significance level of 0.20, requires 45 subjects in each treatment group. When adjusted for a drop-out rate of approximately 3% of subjects who will have no post-treatment-baseline efficacy measurement, the required number of subjects to be randomized in the treatment period is 94. To achieve this, the estimated number of subjects to enter the lead in period is 140, after adjusting for an estimated placebo response rate of 25% and drop-out rate of 10% during the lead-in period.

To replace 3 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 approximately 140 to 143.

Efficacy Analysis

Primary efficacy analyses will be based on the intention-to-treat analysis set from enriched population (eITT) which consists of randomized lead-in placebo non-responders receiving at least one dose of study medication and having at least one post-treatment-baseline efficacy measurement.

The JNJ-42165279 treatment group will be compared with placebo using the primary efficacy endpoint: change from treatment-baseline in $HDRS_{17}$ score during the double-blind treatment period. 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 lead-in baseline total $HDRS_{17}$ score as a continuous covariate and a (pooled) center 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 6-week endpoint.

The change from baseline for the key secondary continuous efficacy endpoints (HAM-A_6 score, $HDRS_{17}$ Anxiety/Somatization factor score, HAM-D_6 score and SIGH-A total score) will be analyzed in the same way as for the $HDRS_{17}$ total score.

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

In addition, exploratory efficacy analyses will be performed on the full intention-to-treat analysis set consisting from all the randomized subjects receiving at least one dose of study medication and having at least one posttreatment-baseline efficacy measurement (fITT). Treatment effect for fITT analysis set will be estimated in 2 manners: using the same MMRM model as for the primary efficacy analysis with and without lead-in response status as additional covariate.

Descriptive statistics for values and changes from baseline for all efficacy measures including subscale scores for selected scales at each time point of the double-blind treatment phase will be provided by treatment group and lead-in response status (where applicable) using both: eITT and fITT analysis sets.

Frequency tables for response of depressive and anxiety symptoms (derived from the $HDRS_{17}$ and SIGH-A) will be provided by treatment group and lead-in response status (where applicable) at each time point of the double-blind treatment phase using both: eITT and fITT analysis sets.

Chi square test will be used to test the overall differences between the treatment groups. If deemed appropriate, Cochran–Mantel–Haenszel test with (pooled) center as stratification factor will be performed.

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.

Biomarker and Pharmacogenomic (DNA) Analysis

Baseline biomarker values and CCI [redacted] will be summarized. Exploratory biomarker analyses may include comparison of biomarker measures between CCI [redacted]

The analysis plan and summarized results from both biomarker and pharmacogenomics analyses will be reported separately.

Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis

The relationship between plasma concentrations of JNJ-42165279 and key clinical efficacy outcomes and adverse events will be explored. In addition, corresponding biomarkers CCI [redacted] 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.

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.

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	11
Week (end of)	-4 to 0	0	1	2	3	4	5	7	9	11	12 to 14
Day	-28 to -1	1	7	14	21	28	35	49	63	77	84 to 98
Clinic Visit (C)	C	C	C	C	C	C	C	C	C	C	C
Study Procedures											
Screening/Administrative											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Medical history and demographics	X										
Prestudy therapy/ATRQ [c]	X										
Preplanned surgery/procedure(s)	X										
MINI interview	X										
Study Drug Administration											
Randomization (IVRS or IWRS)		X	X	X	X	X	X	X	X		
Dispense JNJ-42165279 or placebo		X	X	X	X	X	X	X	X		
Drug accountability			X	X	X	X	X	X	X	X	
Safety Assessments											
Physical examination	X									X	X
Neurological examination [s]	X						X		X	X	
C-SSRS	X[q]	X	X	X	X	X	X	X	X	X	
Vital signs[e]	X	X	X		X		X	X	X	X	X
Body temperature	X	X	X		X		X	X	X	X	X
Body weight [f]	X	X	X		X		X	X	X	X	X
Height	X										
Clinical laboratory assessments[g,m]	X	X	X		X		X	X	X	X	X[h]
Serology	X										
12-lead ECG [i]	X	X[d]	X		X		X	X	X	X	X[h]
Urine drug screen	X[j]	X			X			X		X	
Alcohol screen	X	X									

[a] This section has been amended per Amendments INT-1, 2, 3 and 4.

Phase	Screening	Double-Blind Treatment[a]									Posttreatment[b] (Follow up)
										EW[b]	
Visit	1	2	3	4	5	6	7	8	9	10	11
Week (end of)	-4 to 0	0	1	2	3	4	5	7	9	11	12 to 14
Day	-28 to -1	1	7	14	21	28	35	49	63	77	84 to 98
Clinic Visit (C)	C	C	C	C	C	C	C	C	C	C	C
Pregnancy test	X[k]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[k]	
Independent Central Rater assessments											
Validation of the suitability of the subject for enrolment (after review of MINI, ATRQ and $HDRS_{17}$)	X										
Site Clinician-administered assessments											
$HDRS_{17}$ using SIGH-D – performed by clinical site[r]	X	X	X	X	X	X	X	X	X	X	
SIGH-A - performed by clinical site		X	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	X	X	
Patient-reported assessments											
CPFQ		X	X		X		X	X	X	X	
CUDOS-A		X	X		X		X	X	X	X	
SHAPS		X	X		X		X	X	X	X	
MOS Sleep-R		X	X		X		X	X	X	X	
PSS		X	X		X		X	X	X	X	
Self-assessment of treatment experience										X	
Pharmacokinetics											
Blood sample collection for JNJ-42165279[l]				X			X		X	X	
Pharmacogenomics (DNA)											
CCI											
Biomarkers											
CCI											
Ongoing Subject Review											
Concomitant therapy[p]	*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 21 days after last dose intake or early withdrawal.
[c] Prestudy therapy will include all medications taken within the 30 days before screening. ATRQ verified by the independent rater will be used to document the current antidepressant used by the subjects and to determine the optimal dose of the antidepressant.
[d] Triplicate ECG at Day 1 (predose)
[e] Supine blood pressure, pulse, and oral temperature.
[f] Body weight will be measured with subjects lightly clothed.
[g] Serum chemistry, hematology, coagulation and urinalysis. TSH (all subjects) and FSH (only women) at screening only.
[h] Only in case of any clinical significant abnormalities observed at Week 11.
[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. Investigators may perform additional pregnancy testing at their discretion as clinically needed.
[l] 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, 35, 63 and 77) and 2 to 4 hours postdose.
[m] Samples must be collected prior to dosing under fasting conditions whenever possible.
[n] Subjects will be asked to provide a small amount of saliva the night before and upon awakening the morning of the scheduled visit.
[o] A venous blood sample will be collected for the FAAs (AEA, PEA and OEA). The Visit 2 sample must be taken before the first dose of JNJ-42165279 /placebo.
[p] Concomitant therapies must be recorded throughout the study beginning with signature of the ICF to the final follow up visit (Visit 11).
[q] Baseline version completed at screening.
[r] $HDRS_{17}$ anxiety/somatization factor score determined from the assessment.
[s] A neurological examination will also be completed in case of adverse event of interest.
[t.] 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.

ATRQ = Antidepressant Treatment Response Questionnaire; **CGI-I**=Clinical Global Impression – Improvement; **CPFQ**=Cognitive and Physical Functioning Questionnaire; **C-SSRS** = Columbia Suicide Severity Rating Scale; **CUDOS** = Clinically Useful depression Outcome Scale; **EW** = Early Withdrawal; **HAM-A6** = Hamilton Anxiety Rating scale; **$HDRS_{17}$** = Hamilton Depression Rating Scale; **MINI** = Mini International Neuropsychiatric Interview; **MOS Sleep-R** = Medical Outcomes Study Sleep-Revised; **PSS** = Perceived Stress Scale; **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 9.4.3 and questionnaires are defined after the Time and Events Schedule.

AEA	anandamide
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
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 (5th 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
MINI	Mini International Neuropsychiatric Interview
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
SNRI	Serotonergic/noradrenergic reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment emergent adverse event
TES	Time and Event Schedule

ULN	Upper Limit of Normal
Vss	Volume of distribution at steady state
WBC	White blood cell

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 CCI mg and a multiple dose regimen of 100 mg once-daily (q.d.) 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.

A phase 2a study in patients with social anxiety disorder (SAD) 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[a]

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.

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

Nonclinical effects of JNJ-42165279 have 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 [redacted] μM in the human ether-a-go-go related gene (hERG) patch clamp assay [redacted] and at [redacted] 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 [redacted] mg/kg (C_{max} = [redacted] ng/mL; [redacted]-fold margin over the projected efficacious dose in humans of [redacted] ng/mL) did not induce relevant changes in cardiovascular, electrocardiographic, or respiratory parameters. At the highest dose of [redacted] mg/kg (mean plasma exposure of [redacted] ng/mL), a [redacted]% [redacted] in heart rate was observed in one dog, and a [redacted]% [redacted] 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, [redacted] were noted from [redacted] mg/kg, with changes in sensory-motor and affective responses at [redacted] mg/kg.

Pharmacokinetics and Product Metabolism in Animals

JNJ-42165279 has [redacted] oral bioavailability in rats ([redacted]%), dogs [redacted]%), and monkeys ([redacted]%). After intravenous administration, clearance was [redacted] in the dog and monkey [redacted] mL/min/kg, respectively) and [redacted] in the rat ([redacted] mL/min/kg); the volume of distribution at steady state (Vss) was [redacted]; and the half-life ranged from [redacted] 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 [redacted] in the rat and [redacted] in the dog.

JNJ-42165279 is primarily metabolized by [redacted] in liver microsomes with multiple metabolites observed in vitro and in vivo. [redacted] metabolites formed in [redacted] were [redacted] detected in vitro or in vivo in the toxicology species investigated. 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 [redacted]

CCI and CCI and the CCI (decreased CCI and abnormal CCI) were observed. In female rats, microscopic changes were observed in the CCI CCI while there were no CCI mg/kg. Based on these findings, the no observed adverse effect level (NOAEL) CCI and was CCI mg/kg in female rats. Relative to exposures at the anticipated clinically effective dose of CCI , C_{max} and AUC exposures in the female rats provide CCI -fold and CCI -fold margins respectively. In dogs, doses of CCI mg/kg were well tolerated, while adverse effects at CCI mg/kg were noted in the CCI with CCI CCI or CCI that correlated with CCI CCI CCI Based on these findings, the NOAEL in dogs was CCI providing C_{max} and AUC margins of at least CCI -fold and CCI -fold CCI

Reproductive and embryo-fetal safety was evaluated in rats and rabbits. Male rats treated with JNJ-42165279 for 4 weeks had significantly CCI and CCI number of CCI at doses of CCI mg/kg but not at CCI mg/kg; these changes were fully reversible following a 4-week recovery period. JNJ-42165279 at the high dose of CCI mg/kg, but not at CCI mg/kg, induced changes in CCI . These changes as well as those on CCI are considered exaggerated effects of FAAH inhibition. The C_{max} (CCI ng/mL) and AUC (CCI ng.h/mL) exposures in male rats at CCI mg/kg (the NOAEL for CCI findings) provide margins of CCI and CCI -fold over the anticipated human effective levels. In pregnant rats and rabbits, JNJ-42165279 CCI . There were no CCI . In rabbits, the NOAEL for fetal toxicity was the highest dose tested, offering C_{max} and AUC margins of over CCI -fold. Rat fetuses from pregnant rats treated with CCI 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 CCI mg/kg and associated exposures provide C_{max} and AUC margins of CCI and CCI -fold respectively. No CCI 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 eighth 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_{∞}, increased with increasing dose. Plasma JNJ-42165279 concentrations declined in a CCI with mean $t_{1/2}$ values of CCI to CCI hours for doses of 2.5 to 250 mg.

The effect of CCI on the pharmacokinetics of JNJ-42165279 was investigated at the C -mg dose level. The CCI was CCI based on median t_{max} values of CCI hours and 0.5 hours in the CCI, respectively. On average, the C_{max} values were C % CCI and AUC_{∞} values were C % CCI when JNJ-42165279 was CCI. These CCI CCI.

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_{τ} values were 1.13-times and 1.44-times higher on Day 6 relative to Day 1. The similarity between the mean AUC_{∞} following the 100-mg dose during Part 1 (8,419 ng.h/mL) and the mean AUC_{τ} 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 (SAEs), 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, five cohorts were studied: healthy males at 10 mg, 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 and cerebrospinal fluid (CSF) sampling was conducted prior to dosing and after 7 days of dosing in the healthy male cohorts. Concentrations of JNJ-42165279 in plasma, urine, and 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 OEA concentrations in CSF by approximately 6-fold in all dose groups while mean AEA increases were dose dependent. CSF AEA increased approximately 28-fold, 41 fold, and 77 fold while taking 10 mg, 25 mg, and 75 mg respectively, relative to predose. The concentrations of AA in CSF decreased slightly in all groups including placebo.

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 six 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 elevations of liver transaminases relative to baseline (up to 2.5 times the upper limit of normal[ULN]) that returned to normal after dosing stopped. No increases occurred in ALP or bilirubin. Two out of six subjects taking 10 mg had elevations of ALT up to 1.5 times the ULN that returned to normal after dosing was stopped. No such increases were observed in the 25 mg or 75 mg male cohorts. 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 CCI-mg CCI from Day 4 to Day 10 (inclusive). Subjects also received a dose of 30-mg JNJ-42165279 along with CCI mg CCI on Day 8.

Mean plasma JNJ-42165279 concentrations were CCI over the entire PK sampling period after co-administration of JNJ-42165279 with CCI compared with administration of JNJ-42165279 alone. Plasma JNJ-42165279 concentrations CCI, with median t_{max} values of CCI hour following administration of JNJ-42165279 CCI.

Mean $t_{1/2}$ was approximately CCI% CCI after JNJ-42165279 was co-administered CCI, compared with JNJ-42165279 administered CCI The estimated geometric mean ratios (GMRs) of JNJ-42165279 C_{max}, AUC_{last}, and AUC_{∞} CCI relative to JNJ-42165279 CCI were CCI%, CCI%, and CCI%, respectively. These results indicate that CCI in the CCI of JNJ-42165279 and that CCI is CCI of JNJ-42165279 in CCI

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.

The CCI of JNJ-42165279 administered as a C CI -mg tablet relative to a C CI -mg CCI was evaluated in healthy male subjects under CCI (Study 42165279EDI1005). Mean plasma JNJ-42165279 concentrations CCI CCI after administration of JNJ-42165279 as a CCI The mean AUC and C_{max} values between the CCI The estimated geometric mean ratios (GMRs) of JNJ-42165279 C_{max}, AUC_{last}, and AUC_{∞} for the JNJ-42165279 administered as CCI were CCI%, CCI%, and CCI%, respectively. The time to achieve maximum plasma concentration (t_{max}), terminal half-life values, and intersubject variability were CCI.

A fMRI study with a dose of 100 mg once-daily over 4 days in healthy young males (study 42165279ANX1001) 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, fear and anxiety responses and resilience to stress. Modulation of depression, 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. The net effect of JNJ-42165279 is hypothesized to be a normalization of neurotransmission associated with states of hyper-arousal and chronic stress. JNJ-42165279 is being developed as a possible treatment of disorders of the central nervous systems (CNS), including anxiety disorders, post-traumatic stress disorder (PTSD), and major depressive disorder (MDD) with anxious distress. Based on nonclinical data, the compound is expected to show stress-reduction and anxiolytic activity and, therefore, may also be expected to be potentially effective in the treatment of MDD with anxious distress. The current study will be conducted to assess the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of treatment with adjunctive JNJ-42165279 in subjects with MDD with anxious distress.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy in terms of reduction of symptoms of depression and anxiety, as assessed by the change from baseline on a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$), and overall safety and tolerability of treatment with adjunctive JNJ-42165279 compared to placebo in subjects with MDD with anxiety symptoms who have had inadequate response to treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonergic/noradrenergic reuptake inhibitor (SNRI).

Secondary Objectives

The secondary objectives of this study are:

To assess the efficacy of JNJ-42165279 on core symptoms of anxiety ($HAM\text{-}A_6$).

To assess the efficacy of JNJ-42165279 using dimensional analyses of both anxiety and depression ($HDRS_{17}$ and SIGH-A).

To assess the efficacy of JNJ-42165279 on the response and remission of depressive and anxiety symptoms (derived from $HDRS_{17}$ and SIGH-A).

To assess the plasma pharmacokinetic (PK) profile of JNJ-42165279 administered as once daily (*qd)* in male and female subjects with MDD with anxious distress using a population PK approach and explore its relationship with efficacy and safety parameters.

Exploratory Objectives

The exploratory objectives are:

To evaluate the impact of treatment with adjunctive JNJ-42165279 compared to placebo on Clinical Global Impression (CGI) and exploratory clinician-rated and patient-reported assessments (CUDOS-A, CPFQ, SHAPS, MOS Sleep-R, PSS and Self-Assessment of Treatment Experience).

To explore for [redacted] in subjects with [redacted] features and subjects with [redacted], as reported on the [redacted]

To explore [redacted] (including but not limited to [redacted] and [redacted] that may be related to [redacted] of JNJ-42165279.

To explore the relationship between plasma PK and plasma concentrations of FAAs (anandamide [AEA], palmitoylethanolamide [PEA] and oleoylethanolamide [OEA]) in subjects with MDD with anxious distress.

2.2. Hypothesis

The primary hypothesis is that 6-weeks of treatment with adjunctive JNJ-42165279 is superior to placebo in improving symptoms of depression and anxiety, as measured by the change from baseline in the $HDRS_{17}$, in subjects with MDD with anxiety symptoms who have had an inadequate response to an SSRI/SNRI.

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 in subjects with MDD with anxious distress who have had inadequate response to SSRI/SNRI treatment. Subjects with MDD with anxious distress who have had treatment initiated with an SSRI/SNRI allowed by the protocol will be screened at the investigation site. Site assessments will be reviewed and verified by an independent central rater. The review by a central rater will include the clinical history of MDD, SSRI/SNRI treatment of adequate dose and duration for the current episode of depression, and current symptom severity on the $HDRS_{17}$. Assessments by qualified site personnel including the MINI, ATRQ, and $HDRS_{17}$ will be recorded for review and validation of the suitability of the subject for enrollment into the study by an independent central rater contracted by the sponsor. Subjects who meet the inclusion and exclusion criteria and are enrolled will be maintained on the SSRI/SNRI treatment throughout the study to determine whether adjunctive treatment with JNJ-42165279 can reduce symptoms of MDD with anxious distress. For each subject, the study will consist of three phases: a screening phase of up to 4 weeks, double-blind treatment phase lasting up to 11 weeks, and a 3-week post-treatment (follow up) phase. The double-blind treatment phase of the trial will consist of 3 periods. The first period is a placebo lead-in of double-blind duration, after which subjects will enter the treatment period when they will be randomly assigned to JNJ-42165279 or continuation on placebo for 6 weeks. Subjects who successfully complete the treatment period prior to the end of Week 11, will be treated with placebo for the remaining time of the double-blind phase of the study, which will vary depending on the duration of the placebo lead-in for the specific subject. The total study duration for each subject will be approximately 18 weeks. The end of study is defined as the date of the last visit of the last subject undergoing the trial. Investigators and subjects will

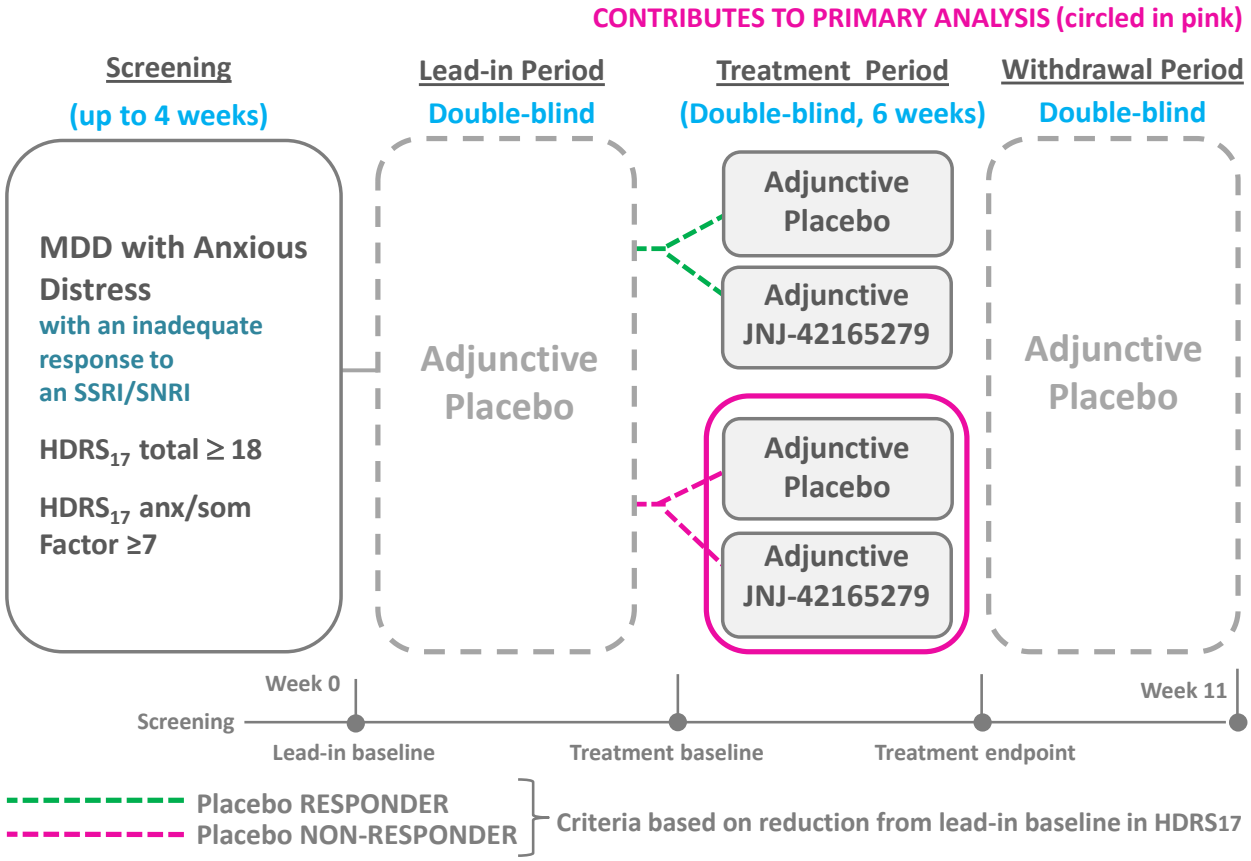
[a] This section has been amended per Amendments INT-1 and 2.

remain blinded to the exact duration of the subject lead-in and withdrawal period during the entire study duration.

Approximately 143 subjects will enter the double-blind placebo lead-in period. At the end of the lead-in period, response status of the subjects will be assessed according to the double-blind response criteria based on reduction in $HDRS_{17}$ relative to lead-in baseline. Both, lead-in placebo responders and lead-in placebo non-responders will be randomly assigned in a 1:1 ratio to either 25 mg of JNJ-42165279 or placebo in the treatment period. The primary efficacy analyses will be based on the treatment period data from the lead-in non-responders (94 subjects).

The study will be an outpatient study.

Subject-Specific Trial Scheme



Screening

After giving written informed consent, subjects may be screened over a period of up to 4 weeks to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study.

A critical element of the screening is determination that subjects must have (1) reached a pre-defined optimal dose based on the Antidepressant Treatment Response Questionnaire – ATRQ (Chandler 2010), (2) received treatment at the optimal dose for at least 6 weeks with their current antidepressant and (3) failed to respond to the current antidepressant therapy. The following antidepressants are permitted: citalopram, escitalopram, sertraline, paroxetine, venlafaxine XR, desvenlafaxine, duloxetine, milnacipram, vilazodone, and vortioxetine.

Subjects will continue to take their SSRI/SNRI treatment at an adequate and tolerated dose (i.e. monotherapy) throughout the study provided it is one of the antidepressants allowed by this protocol. No antidepressant dose changes are permitted from Screening through the end of the study, including the post-treatment phase. Subjects participating in this study must also fulfill the criteria for current/past/recurrent major depressive illness as per Mini International Neuropsychiatric Interview (MINI). Furthermore, subjects with a primary psychiatric diagnosis other than MDD will be excluded (as per the MINI).

For inclusion, subjects must have a $HDRS_{17}$ total score ≥18 and a $HDRS_{17}$ anxiety/somatization factor score ≥7 while having been treated with one of the antidepressants approved in this protocol at an adequate dose and for at least 6 continuous weeks. The clinical history of the current episode of MDD will be assessed by the MINI and supplementary subject validation questions; the lack of response to antidepressant therapy symptom severity will be assessed by the $HDRS_{17}$, and the antidepressant treatment history based on the subject's report during the screening interview by the ATRQ. Each of these assessments will be conducted by qualified personnel at the site at screening and will be recorded to allow independent validation of the suitability of the subject for enrollment by an independent central rater contracted by the sponsor.

Screening will include obtaining informed consent, assessment of study inclusion and exclusion criteria, medical history, physical examination, neurological examination and safety evaluations.

The screening visit may be split into 2 visits.

Adverse events will be collected starting after the informed consent form (ICF) has been signed until the final study procedure at the final visit.

Subjects who are deemed eligible for randomization will enter the double blind treatment phase.

Double Blind Treatment Phase

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

Lead-in period

Subjects who successfully complete the screening will visit the clinical site/unit on Day 1 and will be treated with placebo for the entire duration of the lead-in period. Investigators and subjects will be blinded to exact duration of each subject-specific lead-in period throughout the study.

Treatment period

At the end of the lead-in period both: placebo lead-in responders and placebo lead-in non-responders will be randomized to receive either adjunctive placebo or JNJ-42165279 in a 1:1 ratio for a 6 week in treatment period.

Investigators and subjects will remain blinded to exact timing of the randomization and study drug treatment assignment for each subject.

Withdrawal period

Subjects who successfully complete the treatment period prior to the end of Week 11 will enter withdrawal period where they will be treated with placebo for the remaining time of the double-blind phase of the study, which will vary depending on the duration of the placebo lead-in for a given subject. Investigators and subjects will be blinded to exact duration of each subject-specific withdrawal period.

During the double-blind 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 (PD) effects will be explored at the time points listed in the Time and Events Schedule (TES).

A pharmacogenomic blood sample will be collected to assess whether the subject is carrier of the A-allele variant for FAAH and to identify genetic and/or epigenetic 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 21 days following last dosing (Week 11), 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]

Blinding, Control, Study Phase/Periods, Treatment Groups

Double-blind placebo lead-in period will be used to enrich the population in the treatment phase and minimize the impact of the expectation bias on the part of subjects and investigators on treatment effect. 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. 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. Placebo lead-in responders will also be randomized to active or placebo during the treatment period in order to expose more subjects to JNJ-42165279 and to obtain the estimate of its effect in general population (not only in enriched). Withdrawal placebo period will be used to aid the blinding of the lead-in period duration and exact beginning and ending of the treatment

[a] This section has been amended per Amendments INT-1 and 4.

period and will allow exploration for indication of symptoms of withdrawal from treatment with JNJ-42165279 including re-emergence of symptoms.

Blinding of the lead-in and withdrawal period duration, exact point of randomization and treatment assignment will be used to reduce potential expectation bias from subjects and investigators during evaluation of clinical endpoints as well as adverse events.

The duration for random assignment to active treatment is 6 weeks. Four weeks is accepted as the minimum time to demonstrate a response to adjunctive treatment of MDD for medications with known clinical effects such as atypical antipsychotics. Extending this to 6 weeks allows for the possibility that a beneficial response to this untested mechanism of action accrues over time and limiting it to 6 weeks permits a period of observation after withdrawal of treatment while remaining under double-blind conditions.

Population

The target population for this study is male or female subjects with MDD with anxious distress who are at least 18 years old but less than 65 years old and have had inadequate response to SSRI/SNRI treatment. The definition of inadequate response is similar to that used in the STAR*D study and adopted in the MGH Antidepressant Treatment History Questionnaire (ATRQ) namely, failure to have a 50% or greater reduction in symptom severity after at least 6 weeks of treatment with adequate doses of a medication which has demonstrated efficacy in clinical trials (Rush et al 2006, Chandler et al 2010). As ascertainment of the degree of symptom improvement will rely on clinical history, failure to show an adequate response will be defined as subjects with MDD who have been treated for a current episode with adequate doses of SSRI/SNRI treatment for at least 6 weeks and manifest depressive symptom severity as measured by the total score $HDRS_{17}$ ≥18. The presence of MDD with anxious distress will be defined by those subjects also having anxiety symptom severity as measured by the anxiety/somatization factor score of the $HDRS_{17}$ ≥ 7 (Fava 2008; Cleary 1977).

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 and each study visit during the double-blind phase. 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.

Rationale for Dose Selection

Based on preclinical models of efficacy with adjustment for differences in affinity of JNJ-42165279 for human FAAH, the exposure predicted to provide 90% maximal effect was 80 ng/mL (Investigator's Brochure), and is hypothesized to be a function of complete (>90%) inhibition of FAAH. Mean steady state plasma concentrations above 80 ng/ml were sustained for up to 12 hours post-dose by 25 mg in the MAD study (42165279ED1002). Suppression of FAAH activity in WBC occurs rapidly after single doses as low as 2.5 mg, and shows dose dependent recovery. The lowest single dose completely suppressing FAAH WBC activity throughout the dosing interval in the single ascending dose study was 30 mg (42165279ED1001), and this was confirmed by complete suppression of FAAH WBC

activity throughout the dosing interval during once-daily dosing at 25 mg in 42165279ED1002. In the same study, increases in concentrations of AEA and OEA in CSF were observed after 7 days of dosing with 10 mg, 25 mg, and 75 mg. Increases in AEA in CSF were dose dependent, increasing 28 fold during dosing with 10 mg, 41 fold with 25 mg, and 77 fold with 75 mg although the range of effects of 25 mg overlapped with those seen with 75 mg. 86% to 96% 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 and complete blocking of retention occurred after 25 mg and higher doses of JNJ-42165279 in 42165279ED1003. In 42165279ED1002, mild increases in liver transaminases were observed in a few subjects, with up to 2.5-fold increases in ALT in 3 of 12 subjects taking 100 mg, none of the subjects taking 25 mg or 75 mg, and 1.5 fold increases in 2 of 6 subjects taking 10 mg

CCI plays an important role in the metabolic elimination of JNJ-42165279. In the presence of CCI, JNJ-42165279 C_{max}, and AUC_{∞} were CCI% and CCI%, respectively (Study 42165219EDI1004). Polypharmacy is common in the clinical practice of mood disorders, and CCI in this study. While the CCI were observed with C mg, C mg q.d. dose also appears to result in CCI

Based on these results, JNJ-42165279 25 mg q.d. is predicted to result in > 95% inhibition of FAAH activity without significant variability throughout the day and appears to offer the best balance between efficacy and safety.

Efficacy Evaluation

Primary

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

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in subjects diagnosed with depression (Hamilton M 1960) 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).

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

Secondary

HAM-A_6

The HAM-A_6 is a 6-item subscale derived from the original Hamilton Anxiety scale (HAM-A) (Hamilton 1959; Hamilton 1969). Because the HAM-A, like the $HDRS_{17}$, is a multi-dimensional scale, Bech derived a 6-item subscale, the HAM-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), with a score range of 0 to 24. In an analysis of four pooled dose-response trials in generalized anxiety disorder (GAD), a Mokken analysis of the HAM-A_6 yielded Loevinger coefficients above 0.40 individually and combined, indicating that unlike the full HAM-A, the HAM-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-A_6 (which is more in accordance with the DSM-IV criteria for GAD than the full HAM-A), the total HAM-A_6 score is considered a sufficient statistic.

HAM-D_6 subscale

Over the years, the most consistent HDRS factor to measure the core symptoms of depression is the one identified using a clinical global severity measure as the index of validity (Bech 1975). The six items are: depressed mood, guilt feelings, work and interests, psychomotor retardation, psychic anxiety, and general somatics (tiredness and pains), with a score range from 0 to 22. In psychometric studies using item response theory models it has consistently been shown that the sum score of these six items (HAM-D_6), in contrast to the $HDRS_{17}$, is a sufficient statistic (Bech 2002).

$HDRS_{17}$ anxiety/somatization factor

The $HDRS_{17}$ anxiety/somatization factor derived from Cleary and Guy's factor analysis of the HDRS scale, includes six items from the original 17-item version: the items for psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight (Cleary 1977). Anxious depression is often defined as MDD with high levels of anxiety symptoms, as reflected in an anxiety/somatization factor score ≥7 (Fava 2008).

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

This original HAM-A scale assesses the severity of different anxiety-related symptoms (Hamilton 1959; Hamilton 1969) with a score range of 0 to 52. It is the most widely used symptom severity measure for anxiety. Each of the 14 items is rated by the clinician on a 5-point scale ranging from 0 (not present) to 4 (maximum degree). The HAM-A has an inter-rater reliability correlation of r = .74 (Maier et al, 1988) and the internal consistency of the measure is reported to be high with a coefficient alpha of .86 (Clark and Donovan, 1994). The symptoms can be grouped into two clusters: psychic anxiety and somatic anxiety.

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). 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). 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.

Clinical Global Impression – Improvement (CGI-I)

The 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

Clinically Useful Depression Outcome Scale (CUDOS-A)

The CUDOS contains 18 items assessing all of the Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) inclusion criteria for major depressive disorder and dysthymic disorder as well as psychosocial impairment and quality of life. The 16 symptom items are rated on a 5-point Likert scale in order to keep the scale brief. The CUDOS was designed to be brief (completed in less than 3 minutes), quickly scored (in less than 15 seconds), clinically useful (fully covering the DSM-5 symptoms of major depressive disorder and dysthymic disorder), reliable, valid, and sensitive to change.

The content of the CUDOS-A subscale was based on the *DSM-5* criteria for the anxious distress specifier. The 5 symptoms of the anxious distress specifier are as follows: feeling keyed up or tense, feeling restless, having difficulty concentrating because of worry, fearing that something awful might happen, and feeling that one might lose control. The items for the anxious distress specifier were drawn from a larger pool of 113 items assessing symptoms of anxiety. The pool of items was reviewed by clinicians experienced in treating mood and anxiety disorders, and consensus was reached regarding the items assessing the 5 criteria of the *DSM-5* specifier. The respondent rated the 5 CUDOS-A items on the same 5-point ordinal scale used to rate the symptoms of depression (Zimmerman 2014). The CUDOS-A will be included in this trial to determine the correlation between endorsement of the DSM-5 criteria and other symptom assessments in this population and to explore for change as a function of time and/or treatment.

An example of the CUDOS-A is provided in Attachment 3.

Cognitive and Physical Functioning Questionnaire (CPFQ)

The CPFQ is a brief self-report scale that provides additional information regarding the impact of adjunctive treatment on aspects of cognitive function including attention, memory and mental acuity. Subjects with MDD are often reported to have difficulties with functioning in this area.

An example of the CPFQ 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). 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.

Perceived Stress Scale (PSS)

The PSS is a brief, validated self-report scale that was selected to evaluate the impact of treatment with adjunctive JNJ-42165279 compared to placebo on perceived stress in this population.

An example of the PSS is provided in Attachment 6.

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. This questionnaire is an internal Janssen scale.

An example of the Self-Assessment of Treatment Experience is provided in Attachment 8.

Safety Evaluations

Clinical Scales

Columbia Suicide Severity Rating Scale (C-SSRS)

An interview to assess the risk of suicidal ideation and behavior will be conducted at each study visit from Screening through the end of the double-blind treatment phase.

The C-SSRS is a low-burden 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). 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 to 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 9 and Attachment 10 for examples of the C-SSRS (baseline) and C-SSRS (since last visit), respectively.

Pharmacokinetic Evaluations

During the study, the sparse blood samples will be collected at the time points indicated in the Time and Events Schedule for PK evaluation in patient population. 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 PK differences between healthy subjects and subjects with MDD. 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.

Pharmacodynamic 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).

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution, metabolism 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 for genotyping [redacted] which has been [redacted] (Conzelman et al, 2012). Approximately one quarter of the population carries the [redacted]. Genotyping of this gene may [redacted] measured in this study. In addition, pharmacogenomics research may allow for the identification of [redacted] factors that influence the [redacted] of JNJ-42165279 and for the identification of [redacted]. Specifically, [redacted] known to be in [redacted] will be evaluated.

Biomarker samples (blood, saliva) will be collected for the [redacted] (including but not limited to markers related to [redacted] to allow for [redacted] and for an [redacted] evaluation.

DNA and Biomarker samples may be used to help to explain CCI [redacted] or may help to identify population subgroups that respond differently to a drug. DNA and Biomarker 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 subject will be discontinued from the study when the QTc interval (QTcF; QTcB if ECG machine only shows QTcB) 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 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) if the frequency of discontinuations exceeds 10% of subjects or increases in liver transaminases of 5-fold over the ULN are observed. 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[b]

Approximately 143 subjects with MDD with anxious distress will be enrolled in the proof-of-concept study. 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.

[a] This section has been amended per amendment INT-5

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

The inclusion and exclusion criteria for enrolling subjects in this study and the prohibitions and restrictions are described in the following 3 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.

For a discussion of the statistical considerations of subject selection, refer to Section 11.1, 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 MDD with Anxious Distress. Subjects with a diagnosis of comorbid Generalized Anxiety Disorder (GAD), Social Anxiety Disorder, or Panic Disorder may be included, if the investigator considers MDD with Anxious Distress to be the primary diagnosis (confirmed by an independent central rater through review of the MINI interview obtained by the site at screening).

   Subjects must have been treated with an SSRI/SNRI antidepressant approved in this protocol at an adequate dose, as defined by the ATRQ, and for at least 6 continuous weeks, validated by an independent central rater contracted by the sponsor.
3. A $HDRS_{17}$ total score ≥ 18 at screening, assessed by a site rater and validated through review by an independent central rater contracted by the sponsor; and on Day 1 by site rater.
4. A $HDRS_{17}$ anxiety/somatization factor score ≥7at screening, assessed by a site rater and validated through review by an independent central rater contracted by the sponsor; and on Day 1 by site rater.
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 4.

   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

[a] This section has been amended per Amendment INT-1, 3 and 4.

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. Criterion modified by Amendment 4.

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 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. Has any other current major psychiatric condition, including, but not limited to, MDD with psychotic features (lifetime), bipolar disorder (including lifetime diagnosis), obsessive-compulsive disorder, post-traumatic stress disorder, borderline personality disorder, eating disorder (e.g., bulimia, anorexia nervosa), or schizophrenia.

   The MINI will be conducted by the primary investigator/sub-investigator (either a psychiatrist or Ph.D. psychologist) at Screening to confirm MDD as the primary diagnosis. In addition, an independent rater will confirm that the current depressive episode is valid as well as verifying any comorbid psychiatric conditions validated in the MINI. As noted, subjects with a diagnosis of comorbid GAD, Social Anxiety Disorder, or Panic Disorder may be included.

2. Has a length of current major depressive episode (MDE) >6 months.

3. Has initiated psychotherapy specific for MDD (such as cognitive behavioral, behavioral, or interpersonal therapy) for the current episode of depression within 6 weeks prior to screening. Subjects receiving psychotherapy can continue receiving psychotherapy provided this therapy has been stable in frequency for the last 6 months and will remain unchanged throughout the study treatment.

4. Has more than 1 failed treatment with antidepressants of adequate dose and duration in the current major depressive episode, prior to and not including the inadequate response to the current SSRI/SNRI antidepressant.

[a] This section has been amended per Amendments INT-1, 2 and 5.

5. Has a history of resistance to medication treatment of major depressive episodes (≥3 lifetime treatment failures with approved antidepressants at adequate doses and duration).

6. 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.

7. 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.

8. Criterion modified by Amendment 2.

   8.1. 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).

9. Criterion modified by Amendment 5.

   9.1. Subject has a clinically significant abnormal finding on 12-lead ECG such as QTcF (QTcB if ECG machine only shows QTcB) >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.

10. Criterion modified by Amendment 5.

    10.1 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 renal or liver function analytes significantly higher (more than 1.5 times the upper limit of normal) at screening are not eligible for the study.

11. 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).

12. If a subject is using a drug with moderate/strong CYP3A4 inhibiting or inducing properties at, or prior to, screening it must be discontinued within the equivalent of at least 5 half-lives prior to Day 1. Note: an existing medication should not be stopped solely for the purpose of the subject entering the study. Use of moderate and strong inhibitors and inducers of CYP3A4 are prohibited during the study (See Attachment 12).

13. 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.

14. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.

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

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

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

18. 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.

19. Criterion modified by Amendment 5.

    19.1 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.

20. 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.

21. 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.

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

23. 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.

24. 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

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

4.3. Prohibitions and Restrictions

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. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners, if of childbearing potential, should also use an appropriate method of birth control for at least the same duration.

2. Alcohol-containing products are not permitted from 24 hours before scheduled visits to the study site. The use of limited amounts of alcohol (up to 2 drinks daily) during the other days will be allowed.

3. 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.

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

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

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization

Central randomization will be implemented in this study. 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 stratified by (pooled) center and lead-in response status. Exact timing of randomization for each subject will be blinded. The interactive voice/web response system (IVRS/IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the subject. The requestor must use his or her own user identification and personal identification number each time when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject.

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 data review by the DRC is specified (see

Section 11.3), 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 review.

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 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. 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.

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 per Amendments INT-2 and 4.

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.

Subjects will be enrolled contingent on having initiated SSRI/SNRI antidepressant treatment for their current episode of MDD. The following antidepressants are permitted: citalopram, escitalopram, sertraline, paroxetine, venlafaxine, venlafaxine XR, desvenlafaxine, duloxetine, milnacipram, vilazodone and vortioxetine. Subjects will only continue one of these allowed antidepressants at an adequate and tolerated dose (i.e. monotherapy) during the study. No changes in the antidepressant or dose are permitted from Screening through the end of the study, including the post-treatment phase.

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 if they have initiated psychotherapy specific for MDD (such as cognitive behavioral, behavioral, or interpersonal therapy) for the current episode of depression within 6 weeks prior to screening. Subjects who are otherwise receiving long-standing psychotherapy can continue receiving psychotherapy provided this therapy has been stable in frequency for the last 6 months and will remain unchanged throughout the study treatment.

Prohibited Medications

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

[a] This section has been amended per Amendments INT-1, 2 and 5.

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

Psychiatric medications other than the SSRI/SNRIs allowed in the protocol. Prohibited medications include mood stabilizers, antipsychotics, other antidepressants (e.g., MAOIs or TCAs), or medications to treat anxiety (including benzodiazepines: see below)

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, however, not more than 2 nights in a row and not more than a total of 3 nights weekly during the double-blind treatment period.

Other Prohibited Medications include:

- Sedating antihistamines
- Melatonine and ramelteon
- S-adenosyl methionine (SAMe), St. John's wort, ephedra or kava kava
- Opiates, including morphine, codeine hydrocodone, oxycodone, and methadone
- Anticonvulsants
- Moderate and strong CYP3A4 inhibitors or inducers (Attachment 12)

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

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.

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 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. 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 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.

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 300 mL.

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

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:

Physical examination

Neurological examination

Body weight

12-lead ECG

Body temperature

Height

Supine vital signs (systolic and diastolic blood pressure and pulse)

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

C-SSRS (baseline)

Clinical safety laboratory assessments under fasted conditions, when feasible (including serology, hematology, serum chemistry, coagulation, TSH, FSH [women only] and urinalysis)

Urine drug screen

Alcohol screen

All women: Blood and urine pregnancy test

Review of inclusion and exclusion criteria

Complete/Review Medical History and Demographics

Complete/Review Prestudy Therapy (ATRQ) (reviewed and validated by an independent central rater)

Review preplanned surgery/procedures

Mini International Neuropsychiatric Interview (MINI) (reviewed and validated by an independent central rater)

$HDRS_{17}$ using the SIGH-D (reviewed and validated by an independent central rater only at screening)

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 (triplicate)

Body temperature

Supine 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.

CCI [redacted]

Blood and saliva collection for exploratory biomarkers

Urine drug screen

Alcohol screen

[a] This section has been amended per Amendment INT-2 and 4.

Review of inclusion and exclusion criteria

Randomization

Dispense placebo

$HDRS_{17}$ using the SIGH-D

SIGH-A

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

Record adverse events and concomitant medication

Study medication will be dispensed 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 and 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

Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)

Body temperature

Body weight

12-lead ECG

Supine vital signs (systolic and diastolic blood pressure and pulse)

WOCBP: urine pregnancy test.

Randomization

Drug accountability/Treatment compliance will be assessed.

Dispense study drug

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

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.

Randomization

Dispense study drug

Drug accountability/Treatment compliance will be assessed.

C-SSRS

WOCBP: urine pregnancy test.

Blood sample collection for PK of JNJ-42165279 (predose and 2 to 4 hours postdose)

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

Record adverse events and concomitant medication

Week 3 (Day 21)

Subjects will visit the site at Day 21 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 21 as specified in the Time and Events schedule. Assessments can be performed pre-or post dose unless otherwise indicated.

C-SSRS

Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)

Body temperature

Body weight

12-lead ECG

Supine vital signs (systolic and diastolic blood pressure and pulse)

Urine drug screen

WOCBP: urine pregnancy test.

Randomization

Drug accountability/Treatment compliance will be assessed.

Dispense study drug

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

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.

Randomization

Dispense study drug

Drug accountability/Treatment compliance will be assessed.

C-SSRS

WOCBP: urine pregnancy test.

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

Record adverse events and concomitant medication

Week 5 (Day 35)

Subjects will visit the site at Day 35 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 35 as specified in the Time and Events schedule. Assessments can be performed pre-or post dose unless otherwise indicated.

Neurological examination

C-SSRS

Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)

Blood sample collection for PK of JNJ-42165279 (predose and 2 to 4 hours postdose)

Body temperature

Body weight

12-lead ECG

Supine vital signs (systolic and diastolic blood pressure and pulse)

WOCBP: urine pregnancy test.

Blood sample collection for pharmacogenomics

CCI [redacted]

Randomization

Drug accountability/Treatment compliance will be assessed.

Dispense study drug

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

Record adverse events and concomitant medication

Week 7 (Day 49)

Subjects will visit the site at Day 49 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 49 as specified in the Time and Events schedule. Assessments can be performed pre-or post dose unless otherwise indicated.

C-SSRS

Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, coagulation and urinalysis)

Body temperature

Body weight

12-lead ECG

Supine vital signs (systolic and diastolic blood pressure and pulse)

Urine drug screen

WOCBP: urine pregnancy test.

Randomization

Drug accountability/Treatment compliance will be assessed.

Dispense study drug

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

Record adverse events and concomitant medication

Week 9 (Day 63)

Subjects will visit the site at Day 63 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 63 as specified in the Time and Events schedule. Assessments can be performed pre-or post dose unless otherwise indicated.

Neurological examination

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 (predose and 2 to 4 hours postdose)

Blood sample collection for pharmacogenomics

CCI [redacted]

Body temperature

Body weight

12-lead ECG

Supine vital signs (systolic and diastolic blood pressure and pulse)

Randomization

Drug accountability/Treatment compliance will be assessed.

Dispense study drug

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

Record adverse events and concomitant medication

Week 11 (Day 77)

Subjects will visit the site at Day 77 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 77 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 and serum pregnancy test

Urine drug screen

Blood sample collection for PK of JNJ-42165279 (predose and 2 to 4 hours postdose)

Blood sample collection for pharmacogenomics

CCI [redacted]

Body temperature

Body weight

12-lead ECG

Supine vital signs (systolic and diastolic blood pressure and pulse)

Drug accountability/Treatment compliance will be assessed.

$HDRS_{17}$ using the SIGH-D

SIGH-A

CGI-I

CPFQ

CUDOS-A

SHAPS

MOS Sleep-R

PSS

Self-assessment of treatment experience

Record adverse events and concomitant medication

9.1.4. Posttreatment Phase (Follow Up)

Minimally 7 and maximally 21 days following last dosing (Week 11), 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:

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 11

Body temperature

Body weight

12-lead ECG (only in case of any clinical significant abnormalities at Week 11)

Supine vital signs (systolic and diastolic blood pressure and pulse)

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 guidance, 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 9 and Attachment 10 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, supine 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.

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[b]

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:

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

[b] This section has been amended per Amendment INT-4

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 (PT)
- International normalized ratio (INR)

-activated partial thromboplastin time (aPPT)

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
-alkaline phosphatase (ALP)
-creatine phosphokinase (CPK)
-lactic acid dehydrogenase (LDH)
-uric acid
-calcium
- phosphate
-albumin
-total protein
-cholesterol
-triglycerides
-high density lipid protein
-low density lipid protein

-magnesium

TSH (all subjects) and FSH (only women) only at screening

Urinalysis

Dipstick
-specific gravity
-pH
-glucose
-protein
-blood
-ketones
-bilirubin
-urobilinogen
-nitrite
-leukocyte esterase

Flow Cytometry
-RBC
-WBS
-epithelial cells

Sediment
-crystals
-casts
-bacteria

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 breath test

Pregnancy tests:

- In all women: serum β-HCG and urine pregnancy test will be performed at Screening and at study visit 10.
- In WOCBP: serum β-HCG and 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

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

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in subjects diagnosed with depression (Hamilton M 1960) 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).

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[10]; Hamilton 1969[12]). 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) [3], 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-A_6 yielded Loevinger coefficients above 0.40 individually and combined, indicating that unlike the full HAM-A, the HAM-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-A_6 (which is more in accordance with the DSM-5 criteria for GAD than the full HAM-A), the total HAM-A_6 score is considered a sufficient statistic.

HAM-D6

A 6-item subscale from the $HDRS_{17}$ (HAM-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)[4].

$HDRS_{17}$ Anxiety/Somatization factor score

In addition the anxiety-somatization factor total score from the $HDRS_{17}$ will be included (Cleary 1977)[7]. A cut-off of ≥ 7 on this factor has been used to define subjects with anxious depression in prior clinical trials (Fava 2008)[9].

Clinical Global Impression Improvement (CGI-I)

Patient Reported Outcome Assessments

Clinically Useful Depression Outcome Scale (CUDOS-A)

Cognitive and Physical Functioning Questionnaire (CPFQ)

Snaith-Hamilton Pleasure Scale (SHAPS)

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

Perceived Stress Scale (PSS)

Self-Assessment of Treatment Experience

9.3.2. Endpoints

Primary endpoint

Efficacy will be based on the change from baseline of the $HDRS_{17}$ total score with adjunctive JNJ-40411813 compared with placebo after 6 weeks of treatment.

Secondary endpoints

Change from baseline in HAM-A_6 score, $HDRS_{17}$ Anxiety/Somatization factor score, HAM-D_6 score, SIGH-A total score, the distribution of remitters and responders based on $HDRS_{17}$ and SIGH-A total score reduction from lead-in baseline definitions, will be compared with placebo after 6 weeks of treatment.

Exploratory endpoints

Other scales (CGI-I) and patient reported outcomes (CUDOS-A, CPFQ, SHAPS, MOS Sleep-R, PSS and Self-Assessment of Treatment Experience) will be used during the study.

9.4. Pharmacokinetics

9.4.1. 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.

9.4.2. 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.

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.

9.4.3. 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_{τ} area under the plasma concentration-time curve from 0 to τ hours post dosing (time τ 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.

9.5. Biomarker and Pharmacogenomic Evaluations

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).

Blood and saliva will be collected for the assessment of biomarkers at the time points indicated conditions (no food or drink except water for at least 8 hours/overnight) between 08:00 and 10:00 am whenever possible. When fasting is not feasible subjects should be advised to follow a low-fat diet. Subjects should be informed to refrain from strenuous exercise and use of NSAID medications for 24 hours before blood collection (as the use of NSAIDs may impact biomarker measurements, specifically via altering circulating and inducible cytokine levels. In addition NSAIDs also have been reported to inhibit FAAH directly so there is a particular need in FAAH studies to restrict their use). Any exercise performed during 24 hours prior to visit and details of length of fast/food intake prior to collection should be recorded on the CRF or lab requisition form.

In CCI [redacted] (including but not limited to markers related to CCI [redacted] will be investigated to allow for CCI [redacted] and for an CCI [redacted] evaluation. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

CCI [redacted] for the measurement of CCI [redacted] will be collected the evening before and upon awakening the morning of the visits indicated in the Time and Events schedule. Subjects will collect CCI [redacted] Subjects should not CCI [redacted]

DNA samples will be analyzed CCI [redacted].[8] Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data. DNA samples may also be used for the identification of CCI [redacted] that may influence the CCI [redacted] of JNJ-42165279, and for CCI [redacted].

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

The biomarker and pharmacogenomics data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

9.6. 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.

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 11 (Day 77) 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 11 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 11 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. Sample Size Determination[a]

The sample size for the study is determined based on the assumption of a minimally relevant treatment effect size of 0.45 in the mean change from baseline to the endpoint in $HDRS_{17}$ total score between JNJ-42165279 treatment group and placebo. The assumed effect size is based on review of the literature looking at the treatments for MDD and MDD with anxious distress (Lee 2004 and McIntyre 2007) taking into account that the effect size in enriched population is expected to be higher. A standard deviation of 7.5 in the change in $HDRS_{17}$ total score from baseline is estimated based on previously conducted clinical trial in similar patient population (40411813DAX2001) allowing for a higher variability.

The effect size of 0.45 (under SD assumption of 7.5) translates to a treatment difference between JNJ-42165279 and placebo at endpoint of 3.5 points. Detection of this magnitude of effect size with a power of 90% at an overall 1-sided significance level of 0.20, requires 45 subjects in each treatment group. The choice of alpha and beta (1-power) for this Phase study was made in order to increase sensitivity for detecting a therapeutic signal while also maintaining a modest sample size. Thus, power was set to a high value (power=90%; beta=10%) but the type 1 error rate was specified at 1-sided alpha=0.20. This choice is supported by a recent publication by Lindborg et al in which authors note that type 1 and 2 error levels commonly employed in Phase 3 study designs (simple hypothesis tests with 2-sided alpha=0.05 and beta=0.2) are suboptimal for Phase 2, and that switching these values (increasing alpha while decreasing beta) can increase Phase 2 productivity and reduce the risk of rejecting a compound with significant therapeutic potential.

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

When adjusted for a drop-out rate of approximately 3% of subjects who will have no pre-treatment baseline efficacy measurement, the required number of subjects to be randomized in the treatment period is 94. To achieve this, the estimated number of subjects to enter the lead in period is 140, after adjusting for an estimated placebo response rate of 25% and drop-out rate of 10% during the lead-in period.

To replace 3 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 approximately 140 to 143.

Blinded sample size re-estimation is previewed with 180 as maximal number of subjects to be enrolled in the trial (Section 11.4).

11.2. Efficacy Analysis

Primary efficacy analyses will be based on the intention-to-treat analysis set from enriched population (eITT) which consists of randomized lead-in placebo non-responders receiving at least one dose of study medication and having at least one post-treatment baseline efficacy measurement.

The JNJ-42165279 treatment group will be compared with placebo using the primary efficacy endpoint: change from treatment baseline in $HDRS_{17}$ score during the double-blind treatment period. 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 lead-in baseline total $HDRS_{17}$ score as a continuous covariate and a (pooled) center 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 6-week endpoint.

The change from baseline for the key secondary continuous efficacy endpoints ($HAM\text{-}A_6$ score, $HDRS_{17}$ Anxiety/Somatization factor score, $HAM\text{-}D_6$ score and SIGH-A total score) will be analyzed in the same way as for the $HDRS_{17}$ total score.

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

In addition, exploratory efficacy analyses will be performed on full intention-to-treat analysis set consisting of all the randomized subjects receiving at least one dose of study medication and having at least one post-treatment baseline efficacy measurement (fITT). Treatment effect for fITT analysis set will be estimated in 2 manners: using the same MMRM model as for the primary efficacy analysis with and without lead-in response status as additional covariate.

Descriptive statistics for values and changes from baseline for all efficacy measures including subscale scores for selected scales at each time point of the double-blind treatment phase will be provided by treatment group and lead-in response status (where applicable) using both: eITT and fITT analysis sets.

Frequency tables for response of depressive and anxiety symptoms (derived from the $HDRS_{17}$ and SIGH-A) will be provided by treatment group and lead-in response status (where

applicable) at each time point of the double-blind treatment phase using both: eITT and fITT analysis sets. Chi square test will be used to test the overall differences between the treatment groups. If deemed appropriate, Cochran–Mantel–Haenszel test with (pooled) center as stratification factor will be performed.

11.3. 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.

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.

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

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, supine blood pressure (systolic and diastolic), 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.

11.4. Interim Analysis

No interim analysis is foreseen. However, depending on the recruitment, an unblinded review of the data might be conducted for subjects who completed the treatment periods by an internal Data Review Committee (DRC). The DRC may decide to terminate the study after review of the safety data. If any such review is conducted it will be documented in an Early Medicine DRC charter prior to the unblinding. The constitution of the Data review committee will be documented in the Early Medicine Data Review Committee charter and may include sponsor study team members.

Blinded data review for purpose of sample size re-estimation may be performed after 75% of the subjects are randomized. Sample size may be re-adjusted if observed SD substantially deviates from the hypothesized or if the lead-in response and dropout rate substantially deviate from the assumed. Maximal number of subjects to be enrolled in the trial will not surpass 180.

11.5. Biomarker Analysis

Changes in blood and saliva biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in selected biomarkers and clinical endpoints will be explored. Additional exploratory analyses may be performed and results of exploratory analyses may be presented in a separate Biomarkers report.

11.6. Pharmacogenomic Analyses

Results will be presented in a separate report.

11.7. Pharmacokinetic and Pharmacokinetic/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.

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.

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 (like if the frequency of discontinuations exceeds 10% of subjects or increases in liver transaminases of 5-fold over the ULN 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

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

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 11.

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.

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 (e.g., 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 C -mg CCI

The JNJ-42165279 placebo will be supplied as CCI , matching visually to the CCI . 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 11 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 CCI [redacted] 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

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 efficacy of JNJ-42165279 for treatment of MDD with anxious distress is not known and testing for evidence of benefit will require random assignment to active drug or placebo. Introduction of other medication or psychotherapeutic treatment to augment response to their ongoing treatment with SSRI/SNRI monotherapy will not be allowed. Subjects will be monitored for the severity of their major depressive episode including assessment of suicidality to ensure the safety of subjects and confirm whether continuation in the study is in their best interest.

The study treatment duration in this study of subjects with MDD is supported by the available toxicology and clinical data (see Investigator's Brochure)[1]. A safety signal of treatment emergent elevation of liver transaminases up to 2.5 times the upper limit of normal was identified in the Phase 1 multiple dose study, occurring in 5 out of 30subjects exposed to more than 4 days dosing of JNJ-42165279 and 1 out of 10 subjects on placebo, returning to normal values after dosing had ended. 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, concomitant treatment with strong CYP3A inhibitors will not be allowed, and clinical safety labs will be collected at least every 2 weeks with results available for ongoing monitoring by the investigator and sponsor. 'Stopping rules' have been developed for stopping treatment in the event that subjects have an increase in transaminases to >3 x ULN 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 in liver transaminases 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; study medication will be administered adjunctively to SSRI/SNRI therapy. All medication treatment will occur within the context of carefully supervised and supportive care. Only investigators experienced in the treatment of MDD 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.

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

The total blood volume to be collected will not exceed 300 mL, which is considered to be safe and acceptable in comparison to a Red Cross blood donation.

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.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

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 MDD, to understand differential drug responders, and to develop tests/assays related to JNJ-42165279 and MDD. 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[a]

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. Backache, 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.

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

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: Clinically Useful Depression Outcome Scale (CUDOS-A)

INSTRUCTIONS

This questionnaire includes questions about symptoms of depression. For each item please indicate how well it describes you during the PAST WEEK, INCLUDING TODAY.
Circle the number in the columns next to the item that best describes you.

RATING GUIDELINES

0=not at all true (0 days)
1=rarely true (1-2 days)
2=sometimes true (3-4 days)
3=often true (5-6 days)
4=almost always true (every day)

During the PAST WEEK, INCLUDING TODAY....

1. I felt keyed up or on edge because I was worried about things…….....0 1 2 3 4

2. I felt very fidgety, making it difficult to sit still 0 1 2 3 4

3. I had difficulty concentrating because my mind was on my worries…….....0 1 2 3 4

4. I worried a lot that something bad might happen.....0 1 2 3 4

5. When I was extremely anxious, I was afraid I would lose control…….....0 1 2 3 4

Attachment 4: Cognitive and Physical Functioning Questionnaire (CPFQ)

Appendix 1. Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire[a]

Please answer all questions by circling the correct answer or the answer which seems the most appropriate to you (consider "normal" the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning).

a) How has your motivation/interest/enthusiasm been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

b) How has your wakefulness/alertness been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

c) How has your energy been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

d) How has your ability to focus/sustain attention been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

e) How has your ability to remember/recall information been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

f) How has your ability to find words been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

g) How has your sharpness/mental acuity been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

[a]Copyright Massachusetts General Hospital.

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: Perceived Stress Scale (PSS)

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

	0 = Never	1 = Almost Never	2 = Sometimes	3 = Fairly Often	4 = Very Often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Please feel free to use the *Perceived Stress Scale* for your research.

Mind Garden, Inc.
info@mindgarden.com
www.mindgarden.com

References

The PSS Scale is reprinted with permission of the American Sociological Association, from Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 386-396.

Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health.* Newbury Park, CA: Sage, 1988.

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: 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 9: 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 Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you wished you were dead or wished you could go to sleep and not wake up?* If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts 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. *Have you actually had any thoughts of killing yourself?* If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act 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".* *Have you been thinking about how you might do this?* If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan 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".* *Have you had these thoughts and had some intention of acting on them?* If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?* 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. *Most Severe Ideation:* ____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* (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 *When you have the thoughts, how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability *Could /can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents *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?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	___
Reasons for Ideation *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?* (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	___

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: 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. 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. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *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) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: 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).* 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. *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?* If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: 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. *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?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: 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). *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)?* If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: 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: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 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). 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). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 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). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Attachment 10: 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 Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you wished you were dead or wished you could go to sleep and not wake up?* If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts 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. *Have you actually had any thoughts of killing yourself?* If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act 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".* *Have you been thinking about how you might do this?* If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan 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".* *Have you had these thoughts and had some intention of acting on them?* If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?* 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). *Most Severe Ideation:* ____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* (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 *When you have the thoughts, how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability *Could /can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents *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?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	___
Reasons for Ideation *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?* (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	___

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: 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. 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. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *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) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: 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).* 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. *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?* If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: 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. *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?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: 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). *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)?* If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: 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: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 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). 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). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 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). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Attachment 11: 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:

• Suicidal thinking, ideation/ behavior,
• Sleep changes/difficulty sleeping, reduced sleep, abnormal sleep, abnormal sleep, tiredness, fatigue, reduced energy,
• Difficulty in sexual desire, performance or satisfaction,
• Reduced appetite, weight changes (loss or increase),
• Activation or hypomania/ mania,
• Excessive happiness
• Irritability, anger, impulsive behavior,
• Agitation, anxious/anxiety, tension, panic attacks, phobia

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.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

Attachment 12: 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-5 42165279MDD2001

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 intervention, 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

Signatur PPD Date: PPD
(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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Approved, Date: 24 October 2017