An Exploratory Multicenter, Double-Blind, Diphenhydramine- and Placebo-Controlled Safety, Efficacy and Biomarker Study with JNJ-42847922 in Subjects with Major Depressive Disorder.

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Primary Objective:To investigate the safety and tolerability of JNJ-42847922 in subjects with MDD. Study medication will be administered for 10 days in women of childbearing potential (WOCBP) or for 4 weeks in all other subjects.Secondary Objectives...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON42397

Source
ToetsingOnline

Brief title
Multiple dose study to JNJ-42847922 in MDD patients

Condition

- Mood disorders and disturbances NEC

Synonym
Depression, Insomnia

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Clinical pharmacology, Depression, Insomnia

Outcome measures

Primary outcome

- Latency to persistent sleep (minutes)

- Total sleep time (minutes)

- Wake After Sleep Onset (minutes)

- Wake during total sleep period (minutes)

- Wake after final awakening (minutes)

- Sleep efficiency (%)

- Total time spent in deep sleep (duration of slow wave sleep) (minutes)

Secondary outcome

PSG secondary endpoints

- Time in bed (minutes)

- Sleep onset latency (minutes)

- Number of awakenings (#)

- Time to first awakening after sleep onset (minutes)

- REML (minutes)

- Duration of REM sleep (minutes)

- Duration of Stage 1 Sleep (minutes)

- Duration of Stage 2 Sleep (minutes)

- Number of REM blocs (#)

Study description

Background summary

In this study, the safety, tolerability and preliminary efficacy of JNJ-42847922 will be evaluated in subjects with MDD in a multiple dose paradigm. In a prior study, male and female healthy subjects were exposed to ascending dose levels of JNJ-42847922 for 10 days at doses up to 60 mg [42847922EDI1003]. JNJ-42847922 was well tolerated in this study. Furthermore, the effect of JNJ-42847922 on sleep has been evaluated in a single dose study in MDD subjects [42847922EDI1002]. The primary endpoint in that study, LPS, was significantly shortened at all dose levels tested (10, 20, and 40 mg) relative to placebo. The present study is performed to further document the safety and tolerability of JNJ-42847922 in
a subject population of significant clinical interest upon multiple dose administration over 10 or 28 days in preparation of phase 2-studies with longer duration.

Study objective

Primary Objective:
To investigate the safety and tolerability of JNJ-42847922 in subjects with MDD. Study medication will be administered for 10 days in women of childbearing potential (WOCBP) or for 4 weeks in all other subjects.

Secondary Objectives
- To explore the effect of JNJ-42847922 on sleep using the Leeds Sleep Evaluation Questionnaire (LSEQ).
- To explore the effect of JNJ-42847922 on sleep using polysomnography and correlate this with Somno-ART data (when available).
- To explore cognitive and psychomotor function after forced nighttime awakening and after morning awakening using a computerized cognitive test battery.
- To explore the relationship between the effect of JNJ-42847922 on objective sleep parameters (LPS, TST, and Wake After Sleep Onset [WASO] per PSG) and subjective sleep parameters (subjective LPS [sLPS], subjective TST [sTST], and subjective WASO [sWASO] per questionnaire).
- To explore the effect of JNJ-42847922 on symptoms of depression using the structured interview guide for the Hamilton Depression Scale (SIGH-D) and Inventory of Depressive Symptomatology-clinician rated 30 (IDS-C30) (combined in the SIGHD-IDS) and the self-rated Quick Inventory of Depressive Symptoms-16 (QIDS-SR16).

- To explore the effect of JNJ-42847922 on symptoms of rumination using the Ruminative Response Scale (RRS).
- To investigate changes in MDD-realted biomarkers (HPA axis funtion, biomarkers of immune system activation and oxidative stress) in relation to clinical response on depression symptoms and sleep parameters upon treatment with JNJ-42847922 over 10 days of 4 weeks.
- To explore the relationship between changes in secondary endpoints and mechanism-of-action (JNJ-42847922 as OX2R antagonist versus diphenhydramine as H1-reseptor antagonist).
- To investigate the plasma pharmacokinetics of JNJ-42847922.

Study design

This is a multicenter, multiple-dose, double-blind, diphenhydramine- and placebo-controlled study.

Intervention

Subjects will receive one of the following treatments for 10 days (women of childbearing potential) or 4 weeks (rest of the study population) once a day:
-20 mg JNJ-42847922
-25 mg diphenhydramine
-placebo

Study burden and risks

In study 42847922EDI1002, a dose of 20 mg seemed to be optimal in terms of benefit/risk, with the 40-mg dose not demonstrating added benefit on the LPS sleep parameter. Doses higher than 20 mg might induce more pronounced sleep and this may be a safety concern when the compound will be dosed at home. Although the optimal dose range for efficacy in MDD is currently unknown, the 20-mg dose was selected for this study taking into account predicted receptor occupancy, tolerability, and benefit/risk on sleep parameters.

The standard dose of diphenhydramine is 25 mg and therefore this dose has been selected for this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subjects must be men or women, 18 to 64 years of age, inclusive.
2. 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): e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS) in combination with barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; 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 the childbearing potential changes after start of the study (e.g., woman who is not heterosexually active becomes active) a woman must begin a highly effective method of

birth control, as described above.
3. BMI must be between 18 and 30 kg/m2 inclusive (BMI=weight/height2)
4. Subjects must be physically healthy / medically stable on the basis of clinical laboratory tests, medical history, vital signs, and 12-lead ECG performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, retesting of an abnormal lab value(s) that may lead to exclusion will be allowed once during the screening phase. A retest of an abnormal ECG value values will be allowed once in the screening phase. Blood pressure will be the average of
2 measurements.
• The subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.
5. Population specific:
• Subject must meet the DSM-IV or 5 diagnostic criteria for MDD (International Classification of Diseases (ICD)-code F32.x and F33.x), without psychotic features, and confirmed by the MINI 6.0.
• Subject must have an IDS-C30 total score >= 30.
• Subject is either currently antidepressant naive or currently being treated with a maximum of two concurrent antidepressants (refer to list of allowed antidepressants in Attachment 1). If the subject is currently treated with antidepressants, they have to be given at an optimal dose and for at least 4 weeks, but not longer than 24 weeks with a suboptimal response (defined as an IDS-C30 total score >= 30).
6. 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 not donate sperm during the study and for 3 months after receiving the last dose of study drug.
7. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
8. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she:;1. Has current signs/symptoms of, liver or renal insufficiency; hypothyroidism or hyperthyroidism (a normal thyroid-stimulating hormone [TSH] is required at screening; subjects with hyperthyroidism who are on stable treatment with normal TSH may participate but subjects with thyroid supplementation for antidepressant purposes are not allowed in the study), significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, inflammatory (e.g., rheumatoid arthritis, inflammatory bowel disease, Crohn*s disease), or metabolic disturbances. Subjects with diabetes mellitus (type I and II) are not allowed to

participate in the study.;2. Is pregnant or breast feeding.;3. 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 concurrence with the sponsor's study responsible physician, is considered cured with minimal risk of recurrence).
4. Has a primary DSM (4th or 5th edition) diagnosis of general anxiety disorder (GAD), panic disorder, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), anorexia nervosa, or bulimia nervosa. Subjects with comorbid GAD, social anxiety disorder (SAD), or panic disorder for whom MDD is considered the primary diagnosis are not excluded.;5. Has a length of current major depressive episode (MDE) >24 months despite adequate treatment.;6. Has failed more than 2 treatments with a different pharmacological mode of action despite an adequate dose and duration during a previous, or the current depressive episode.;7. Has a current diagnosis of a psychotic disorder, MDD with psychosis, bipolar disorder, an eating disorder, mental retardation, cluster B personality disorder (e.g., borderline antisocial, narcissistic personality disorders), narcolepsy, obstructive sleep apnea/hypopnea (apnea/hypopnea index >10), central sleep apnea, sleep-related hypoventilation, circadian rhythm sleep-wake disorders, restless legs syndrome (periodic leg movements with arousal index >15), substance/medication-induced sleep disorder or parasomnias (NREM sleep arousal disorders, nightmare disorder, REM sleep behavior disorder).;8. 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 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 of any sort, 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.;9. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug, or has participated in 2 or more interventional clinical studies in the previous
1 year, or is currently enrolled in an interventional study.

10. Subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.;11. Subject has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.;12. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.;13. Subject has a history of drug or alcohol abuse or dependence according to DSM-IV or 5 criteria, except nicotine or caffeine, within 6 months before Screening. However, subjects who have completed a treatment for (alcohol) addiction more than 8 weeks prior to first dose administration and are under continuous control of the study center, may be included if the risk to fall back is considered minimal and no significant abnormalities are shown in clinical laboratory or other predose safety assessments.;14. Subject has positive test result(s) for alcohol or drugs of abuse (including barbiturates, methadone, opiates, cocaine, cannabinoids, amphetamine/methamphetamine, benzodiazepines and ecstasy) at Screening.;- Subjects with a positive alcohol or drug screen at Screening may have the test repeated once during the screening phase, based on the investigator's discretion. This determination, and the reason for permitting a repeat test, must be recorded in the subject's

source documents and initialed by the investigator. A positive, repeat alcohol or drug screen is exclusionary.;15. Subject has used:;- Monoamine oxidase inhibitors (MAOIs) within 12 weeks before screening
- A known inhibitor or inducer of CYP3A4 or CYP2C9 activity (e.g., erythromycin, clarithromycin, ketoconazole, itraconazole) within 14 days or a period less than 5-times the drug*s half-life, whichever is longer, before the first study drug administration on Day 1
- St. John*s wort, ephedra, ginkgo, ginseng, or kava within 2 weeks before screening.;16. Subject is unable to stop the following medication from screening and throughout the study:
- Any hypnotics including but not limited to:
- Benzodiazepines
- Sedating antihistamines, including chronic use of diphenhydramine.
- Zolpidem, zoplicon, eszopiclone and ramelteon
- S-adenosyl methionine (SAMe)
- Melatonin
- Antipsychotic drugs (D2-antagonists)
- Lithium and other mood stabilizers
- Opiates
- Drugs which are primarily metabolised by CYP2D6, such as metoprolol and venlafaxine.;17. Is unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy access.;18. Has a contra-indication for the use of diphenhydramine.;19. Is not able to swallow capsules whole.

20. Is unable to read and understand the consent forms and patient reported outcomes, complete study-related procedures, and/or communicate with the study staff.;21. 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.;22. Subject has had major surgery, (e.g., requiring local or general anesthesia) within 12 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.;23. Is a vulnerable subject (e.g., a person kept in detention).;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.;NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results) after screening but before first dose of study drug is given such that they now meet an exclusion criterion, they should be excluded from participation in the study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-07-2015
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	JNJ-42847922
Generic name:	JNJ-42847922
Product type:	Medicine
Brand name:	Nytol
Generic name:	Diphenhydramine

Ethics review

Approved WMO Date:	20-04-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	12-05-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-005182-75-NL
CCMO	NL53141.056.15