A 3-Part, Randomized, Placebo-controlled, Double-blind, Single Ascending Dose Study to Investigate Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of JNJ69095897 in Healthy Participants

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Primary objectives:1. To investigate the safety and tolerability of JNJ-69095897 versus placebo after administration in healthy participants.2. To characterize the PK of JNJ-69095897 in blood, plasma, cerebrospinal fluid (CSF) and urine after...

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

Summary

ID

NL-OMON52349

Source
ToetsingOnline

Brief title
A*Study to*Investigate*Safety and*Pharmacokinetics of JNJ-69095897

Condition

- Mood disorders and disturbances NEC

Synonym
low mood, Mood disorders

Research involving

Human

Sponsors and support

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

Intervention

Keyword: CSF, FIH, PK, SAD

Outcome measures

Primary outcome

1. Vital signs (heart/pulse rate, systolic blood Pressure, diastolic blood pressure, tympanic body temperature), respiratory rate, clinical labs (chemistry, hematology, urinalysis, coagulation [Part 3 only]), adverse events (AE), electrocardiogram (ECG) and Holter recordings.

2. Blood, plasma, CSF, and urine concentrations of JNJ-69095897 and possible metabolites

Secondary outcome

1. Plasma 2-AG levels.

2. Plasma, blood and urine concentrations of JNJ-69095897 and possible metabolites.

3. Plasma and CSF 2-AG levels.

Study description

Background summary

The endocannabinoid system is a biological system located both centrally and peripherally and is involved in many physiological processes such as mood, feeding behaviour, pain sensation, reward, stress and anxiety, glucose

metabolism, memory, and sleep.
The endocannabinoids anandamide (AEA) and 2-arachidonylglycerol (2-AG) are retrograde messengers that modulate the presynaptic release of neurotransmitters via cannabinoid-1 receptor (CB1R) and cannabinoid-2 receptor (CB2R) agonism in diverse neurocircuits. Monoacylglycerol lipase (MGLL) is the enzyme responsible for the catabolism of 2-AG into glycerol and arachidonic acid (AA). JNJ-69095897 is a novel, orally available, brain-penetrant, potent, reversible and selective MGLL inhibitor.

Study objective

Primary objectives:
1. To investigate the safety and tolerability of JNJ-69095897 versus placebo after administration in healthy participants.
2. To characterize the PK of JNJ-69095897 in blood, plasma, cerebrospinal fluid (CSF) and urine after administration in healthy participants.

Secondary objectives:
1. To investigate the effect of JNJ-69095897 versus placebo on peripheral metabolite levels.
2. To assess the relative pharmacokinetics of JNJ-69095897 in healthy participants, following a single oral dose in fasted condition or after a high calorie/ high fat breakfast.
3. To assess the relationship between endogenous metabolite levels in plasma and CSF samples from healthy participants.

Exploratory objectives:
1. To investigate the relationship between PK profile and related endogenous metabolite levels in plasma.
2. To characterize the pharmacodynamic (PD) effect of JNJ-69095897 on CNS function.
3. To obtain exploratory biomarker data from healthy participants.
4. Future evaluation of the PK/PD relationship of JNJ-69095897 plasma concentrations and QT interval corrected for heart rate (QTc) following administration in healthy participants.

Study design

The study will be conducted in three parts in healthy male participants (Part 3 also includes WONCBP): Part 1 SAD, Part 2 Food Effect, and Part 3 CSF sampling.

Part 1 will evaluate single-ascending doses of JNJ-69095897 following an overnight fast or after a high fat breakfast using a double-blind, randomized, placebo-controlled, dose-escalating design.

Part 2 will be an open-label study to assess the effect of food intake on

JNJ-69095897 pharmacokinetics. JNJ-69095897 will be administered after an overnight fast or after a high fat breakfast. The dose of JNJ-69095897 to be administered in Part 2, will be determined on the basis of the acceptability of the safety, tolerability and PK of preceding dose levels in Part 1, and will be not be more than the highest dose tested and was considered well tolerated in Part 1.

Part 3 will be a randomized, double blind, single dose study, using serial CSF sampling to investigate the effect of JNJ-69095897 on 2-AG levels in liquor. The dose of JNJ-69095897 to be administered in part 3, will be determined once a dose in Part 1 has been found to be acceptable based on the safety, tolerability and pharmacokinetics of preceding dose levels in Part 1.

Intervention

JNJ-69095897 or placebo, subsequent dose levels are to be determined following satisfactory review of the safety, tolerability, pharmacodynamic and pharmacokinetic data from previous cohorts.

Study burden and risks

The principal mitigations for these potential risks include the maintenance of an appropriate safety margin based on nonclinical study drug exposure, appropriate selection of the trial population, prespecified safety monitoring procedures, and the selection of the trial facility, where close monitoring can be performed and rapid institution of appropriate care can be given. The potential risks can be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical trial.
A potential risk of (pre)syncope was seen in cohort 1-3 of Part 1. To mitigate this risk, several safety measures were implemented in the study and the exclusion criteria were adjusted to exclude participants who are at a higher risk of (pre)syncope.
In addition to the potential risks associated with study drug administration, there is minimal risk associated with trial procedures including scheduled, periodic venipuncture (limited to < 500 mL) and non-invasive procedures including vital sign assessments, electrocardiograms (ECGs), Holter an telemetry and PD assessments. Subjects are exposed to risks associated with the insertion, indwelling an removal of a spinal catheter in Part 3. To lower these risks, a population of older subjects was chosen, the catheter will be inserted by a trained physician and close monitoring will be performed in the trial facility. Overall, the benefit-risk profile is considered appropriate for this trial.

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

Part 1 and 2: Males with a minimum age of 18 years and maximum age 55 years inclusive,
Part 3: males or female (women of non childbearing potential) with a minimum age of 35 years and a maximum age of 75 years inclusive,

-Healthy based on physical examination, medical history, vital signs, and 12-lead ECG (means of triplicate ECG, incl. QT corrected according to Fridericia's formula (QTcF) <= 450 msec for males and <= 470 msec for females) performed at screening and admission to the clinical unit. Minor abnormalities in ECG, blood pressure and heart rate, which are not considered to be of clinical significance by the investigator, are acceptable, with the exception of bradycardia <= 45 bpm on 12-lead safety ECG, that will be exclusionary at

screening, admission to the clinical unit or prior to the first dose on the dosing day.
-Healthy based on clinical laboratory tests performed at screening. If the results of the serum chemistry panel including liver enzymes, hematology, or urinalysis are outside the normal reference ranges, the participant may be included at the discretion of the investigator, provided the investigator judges the abnormalities to be not clinically
significant. This determination must be recorded in the participant's source documents and initialed by the investigator.
-Participant has a body mass index (BMI) between 18.0 and 30.0 kg/m2 inclusive (BMI=weight/height2).
Please see protocol for remaining inclusion criteria.

Exclusion criteria

1. Has a history of or current significant medical illness including (but not limited to) cardiac arrhythmias or other cardiac disease, orthostatic hypotension, liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances. or any other illness that the investigator considers should exclude the participant.
2. Has a diagnosis or suspicions of any sleep disorder in the last 6 months or current complaints of sleep disturbance, irregular sleep schedule or shift work; habitual daytime naps; travel across time zones in the last 4 weeks or daytime symptoms attributable to unsatisfactory sleep.
3. Has a history of or current major or clinically relevant psychiatric disorder as classified according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) (e.g., mood, anxiety disorders, psychotic disorder etc.).
4. Has a current or recent (within the past year) history of clinically significant suicidal ideation (corresponding to a score of >= 3 for ideation) or any suicidal behavior within the past year, as validated on the C-SSRS at screening or baseline. Participants with a prior suicide attempt of any sort, or history of prior serious suicidal ideation/plan should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.
5. Has known allergies, hypersensitivity, or intolerance to study intervention or its excipients.
6. Has a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing compared with blood pressure from the supine position, during orthostatic blood pressure measurements at screening or baseline.
7. Has 3-second or more pauses in 12-lead ECG Holter based on 24 hours Holter monitoring conducted at screening
8. Has a personal or family history of recurrent (exertional) syncope or

presyncope.
9. Has previously experienced vasovagal syncope's.

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):	16-06-2021
Enrollment:	121
Type:	Actual

Ethics review

Approved WMO Date:	11-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2021

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2023
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	EUCTR2021-000609-26-NL
CCMO	NL77617.056.21
Other	t.b.d.