A Placebo- and Active-Controlled Study to Evaluate the Effects of a Single-Dose and Repeat-Administration of Intranasal Esketamine on On-Road Driving in Subjects With Major Depressive Disorder

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Primary ObjectiveTo evaluate the effect of a single 84-mg dose of intranasal esketamine compared to placebo, on next day driving performance and repeated administration of 84 mg intranasal esketamine on same-day driving performance as assessed by…

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

Summary

ID

NL-OMON43083

Source
ToetsingOnline

Brief title
DriveSaFe2

Condition

- Mood disorders and disturbances NEC

Synonym
depression, Major depressive disorder

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Esketamine

Outcome measures

Primary outcome

On-the-road driving test

In each study period, a validated car driving test will be performed at a predetermined time after dosing. The subject*s task will be to operate a specially instrumented vehicle over a 100-km primary highway circuit, while maintaining a constant speed (95 km/h) and steady lateral position between the delineated boundaries of the right (slower) traffic lane. SDLP (cm), ie, the weaving of the car, is the primary outcome variable. Standard deviation of speed (SDS, km/h) will be a secondary variable. Mean lateral position (MLP, +/- cm), and mean speed (MS, km/h) are control variables

Secondary outcome

Karolinska Sleepiness Scale

(KSS), a subject-reported assessment used to rate sleepiness on a scale of 1 to 9, ranging from *extremely alert* (1) to *very sleepy, great effort to keep awake, fighting sleep (9).

Subjective assessments of driving performance

the perceived quality of their driving performance on a visual analog scale

from 0 (*I drove exceptionally poorly*) to 20 (*I drove exceptionally well*) around a midpoint of *I drove normally*.

A pharmacogenomic blood sample (10 mL) will be collected on Day 1 from all subjects for analysis of cytochrome P450 CYP2B6.

Safety and tolerability will be assessed from the time of consent until the end of the study. Safety and tolerability assessments will include: adverse events, 12-lead electrocardiograms (ECGs), vital signs, clinical laboratory results, and physical examinations. The C-SSRS will be performed to assess suicidal ideation and behavior, and the CADSS will be administered to assess treatment-emergent dissociative symptoms.

Study description

Background summary

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved medications and widely used for the induction and maintenance of anesthesia via intramuscular or intravenous administration. The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors. The antidepressive mechanism of action of ketamine and esketamine is distinct from conventional monoaminergic treatments. Ketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor release, and stimulates synaptogenesis.

Due to the higher NMDA receptor affinity of esketamine over arketamine (R-ketamine), Janssen Research & Development is developing esketamine for antidepressant therapy, which can be administered via a non-invasive and rapidly absorbed route (intranassaly).

Study objective

Primary Objective
To evaluate the effect of a single 84-mg dose of intranasal esketamine compared to placebo, on next day driving performance and repeated administration of 84 mg intranasal esketamine on same-day driving performance as assessed by the mean difference of standard deviation of lateral position (SDLP) from an on-road driving test.

Secondary Objectives
To evaluate the effect of esketamine on:
- Subjective driving ability and mental effort scale
- Karolinska Sleepiness Scale
- Efficacy measured by the Montgomery Asberg Depression Rating Scale (MADRS)
- Safety and tolerability with special attention to:
a. Effects on suicidal ideation/behavior measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
b. Effects on dissociative symptoms using the Clinician-Administered Dissociative States Scale (CADSS)

To evaluate the potential relationship between changes in driving performance and the plasma concentration of esketamine and noresketamine.

Study design

This is a placebo- and ethanol-controlled, single-center study in men and women with MDD consisting of 2 parts.
The total duration of the study is up to 98 days. This includes a screening period of 21 days, a Part A consisting of three 2-day periods with 5 to 14 days of washout between each study drug administration, the next day, a drive test is performed after the administration of ethanol, the positive control, or placebo. Part B consists of 25 days, with 5 to 14 days of washout between the last dose in Part A and the first dose in Part B. Administration of the study medciation takes place on day 4,8,11,15 and a skills test is performed on day 1,11,18 and 25. End-of-study procedures that will take place 7 to 10 days after the last dose in Part B.

Intervention

In Part A, intranasal esketamine or placebo (according to the sequence to which the subject randomized) will be administered on Day 1 of each period as follows: each 28-mg dose of esketamine will be self-administered as 2 sprays totaling one 100-µL of solution into each nostril at Time 0, 5, and 10 minutes for a total of 84 mg. Sprays to each nostril should occur in rapid succession (ie, no waiting between sprays in each nostril at each time point). Oral ethanol or placebo will begin to be administered 45 minutes before the scheduled start of the driving test on Day 2.

In Part B, intranasal placebo (1 spray of placebo solution in each nostril at Time 0, 5, and 10 minutes) will be administered in the morning on Day 1. Intranasal esketamine will be administered in the morning on Days 4, 8, 11, 15, 18, 22, and 25. The driving test will start 6 hours after administration of intranasal placebo or esketamine on the respective study days.

Study burden and risks

Patients will be exposed to a compound that can cause cognitive and psychiatric symptoms. During the study, regular assessrnents of the safety and tolerability will be made and evaluated. Also, patients will be resident in the research unit for dose administration and supervised by the medical staff of the clinical unit during the study day(s) and brought home. When a patient decides to terminate his/her participation in the study, he/she will not be allowed to leave the clinic within 2 hours after dosing Subjects will be advised not to drive a car themselves or operate machines until at least 24 hours after dosing.

The driving study will be executed using a specially equipped car. A licensed driving instructor (having access to dual controls) guards the safety of the subject during the test. The test vehicle and the test execution will be covered by an insurance.

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

Willing and able to adhere to the prohibitions and restrictions specified in this protocol
If a woman, must have a negative serum beta human chorionic gonadotropin pregnancy test at screening and a negative urine pregnancy test on Day 1 of Period 1 in Part A and prior to study drug administration in Part B
Comfortable with selfadministration of intranasal medication and able to follow instructions provided
Normal visual acuity (corrected or uncorrected)
Based on selfreport, able to consume an amount of alcohol that typically produces a blood alcohol concentration (BAC) of 0.05 percent (that is, 2 to 3 alcoholic drinks ingested within 2 hours on a single occasion)

Exclusion criteria

Current or prior diagnosis of psychosis/psychotic or bipolar disorder
Primary sleep disorder, such as insomnia, requiring pharmacological intervention at Screening
Clinically significant abnormal values for hematology, clinical chemistry, or urinalysis at screening or Day 1 of Period 1 as deemed appropriate by the investigator
Clinically significant abnormal physical examination, vital signs, or 12lead electrocardiogram (ECG) at screening or Day 1 of Period 1 as deemed appropriate by the investigator
History of moderate or severe use disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSMIV or DSM5) criteria within 1 year before screening or positive test result(s) for alcohol and/or drugs of abuse (such as barbiturates, opiates, cocaine, cannabinoids, amphetamines, and benzodiazepines) at screening and Day 1 of Period 1

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-10-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Esketamine
Generic name:	Esketamine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-09-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-10-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2017
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-07-2017
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	EUCTR2016-002424-86-NL
CCMO	NL58993.056.16

Study results

Date completed:	29-06-2018
Results posted:	21-12-2020

First publication
12-07-2019

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File