A double-blind, placebo-controlled, randomized dose-ranging trial to investigate efficacy and safety of intravenous MIJ821 infusion in addition to comprehensive standard of care on the rapid reduction of symptoms of Major Depressive Disorder in subjects who have suicidal ideation with intent

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

Summary

ID

NL-OMON51020

Source
ToetsingOnline

Brief title
CMIJ821A12201

Condition

- Mood disorders and disturbances NEC

Synonym
depression, Major Depressive Disorder in subjects who have suicidal ideation with intent

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV (sponsor/verrichter van het onderzoek)

Intervention

Keyword: Major Depressive Disorder, MIJ821, suicidal ideation

Outcome measures

Primary outcome

Change from baseline in MADRS total score at 24 hours after the start of the

first infusion

Secondary outcome

* Number and severity of treatment-emergent adverse events

(TEAEs), including AEs of special interest in the Core Period

* Proportion of participants meeting response criteria (>=50%reduction from

baseline in MADRS total score) over time in the Core Period.

Proportion of participants meeting criteria

for sustained response (>=50% reduction from baseline in MADRS total score

sustained for a period of at least four weeks) in the Core Period

Proportion of participants meeting remission criteria (MADRS total score of

<=12) over time in the Core Period

Proportion of participants meeting criteria for sustained remission (MADRS

total score of <=12 sustained for a period of at least four weeks) in the Core

Period

Proportion of participants meeting criteria for relapse over all randomized population over fixed period in the Extension Period Proportion of relapsing participants meeting response criteria or remission criteria after the first infusion of MIJ821 retreatment in the Extension Period

* PK parameters of MIJ821 in plasma after 1st infusion described by AUClast, Cmax, Tmax (parameters not limited) and after each infusion described by Cmax and Tmax.

Study description

Background summary

Depression is a serious and life-threatening condition with high rates of morbidity and a chronic disease course. Major depressive disorder (MDD) is the psychiatric diagnosis most commonly associated with suicide. Close to 800,000 people die due to suicide every year worldwide. The time between the onset of suicidal ideation and suicide attempt is often very short and can be minutes or a few days, highlighting the need for urgent intervention and development of novel antidepressant therapies with a rapid onset. Concerted efforts over the past 40 years have led to the introduction of safer, better tolerated, and easier-to-prescribe antidepressants, most notably selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Nevertheless, about 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes (SSRIs, SNRIs, tricyclic antidepressants (TCAs, etc.) and psychotherapy. In addition, the onset to treatment response, even when effective, often takes at least four weeks, leading to greater suffering, expenses, and suicidal risk. There remains an ongoing high need for rapid acting, either more effective or better tolerated treatments that can in an effective way interrupt a depressive episode, reduce suicidality, and also able to prevent future depressive episodes.
Ketamine and esketamine (N-Methyl-D-Aspartate (NMDA) receptor antagonists) have demonstrated a certain level of efficacy and showed a rapid mode of action, their safety profile is not without adverse events that are meaningful for both patients and clinicians. Targeting a specific subset of NMDA receptor (NMDAR) is one approach to potentially mitigate adverse effects of NMDAR inhibition

while retaining antidepressant efficacy.
MIJ821 is a highly potent, selective and reversible low molecular weight NR2B-NMDA receptor NAM. MIJ821 is intended to be studied as a short-term treatment over 6 weeks in conjunction with pharmacological antidepressant SoC treatment, for the rapid reduction of depressive symptoms in adult patients with MDD who have suicidal ideation with intent. This treatment approach is intended to allow these patients to rapidly achieve a significant improvement of their depressive symptoms, and suicidal ideation.

Study objective

The main purpose of the study is to support dose selection for future Phase 3 clinical trials by evaluating the efficacy and safety of four MIJ821 doses (0.0048, 0.016, 0.048 and 0.16 mg/kg) administered every other week by intravenous infusion on top of pharmacological antidepressant treatment, compared with placebo plus pharmacological antidepressant treatment, for the rapid reduction of the symptoms of MDD in participants who have suicidal ideation with intent. In addition, the study will explore the effect of single dose administration of MIJ821 0.16 and 0.048 mg/kg to treat MDD in participants who have suicidal ideation with intent.
The study will also have a 12-month Extension Period to explore durability of the effect of the study treatment and the effect of MIJ821 on relapses rate, as well as safety of repeated MIJ821 administration.

Study design

Double-blind, placebo-controlled, randomized dose-ranging trial. The study consists of a Screening Period (up to 48 hrs), a double-blind Core Period (6 weeks) and an Extension Period (up to 52 weeks) for participants classified as responders or remitters at the End of the Core Period.

Intervention

Intravenous MIJ821 administered as a 40-min infusion in addition to comprehensive standard of care (SoC)

Treatment groups (2:1:2:2:2:2:2 ratio):
- placebo every other week
- MIJ821 0.0048 mg/kg every other week
- MIJ821 0.016 mg/kg every other week
- MIJ821 0.048 mg/kg every other week
- MIJ821 0.16 mg/kg every other week
- MIJ821 0.048 mg/kg single infusion with two subsequent placebo dosages given every other week
- MIJ821 0.16 mg/kg single infusion with two subsequent placebo dosages given

every other week

Study burden and risks

Possible side effects of MIJ821:
• Very common side effects (affect about 1 in every 10 people): feeling dizzy, feeling sleepy, feeling abnormal, increased blood pressure
• Common side effects (affects 1 in every 100 people): dissociative reactions (feeling disconnected from yourself, your thoughts, feelings and things around you), problem with memory, nausea
• ECG changes (with or without symptoms) and suicidal ideation have rarely been reported.
• Risks from an IV include pain, swelling, redness, or infection at the IV site. The side effects reappear within hours of the end of the infusion. If any side effect persists, you may need to stay in hospital for longer for observation until the side effect has resolved or stabilized.

Inconveniences and Risks of Investigation Tests and Procedures:
The examination tests are also used during the usual medical treatment.
• Blood samples: blood samples can hurt or bruise. Sometimes someone faints.
• An ECG from a Holter monitoring causes little or no discomfort of risk.

Participating in the study takes extra time for the subject.

The subject must be hospitalized.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female participants, 18 to 65 years of age (inclusive) body weight from 50 to 120 kg (inclusive) at screening.
3. DSM-5 defined major depressive disorder (MDD) with a current major depressive episode (MDE) without psychotic features at the time of screening based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.) assessed at Screening.
4. Participants must have current suicidal ideation with intent, confirmed by Yes-response to Question B3 AND either Question B10 or Question B11 obtained from the M.I.N.I., assessed at Screening.
5. Current suicidal ideation with intent, confirmed by Yes-response to Question 3 AND either Question 9 or Question 10 obtained from the SSTS at Baseline.
6. Montgomery-Åsberg Depression Rating Scale (MADRS) score >28 at Screening and before randomization on Day 1.
7. Participants must agree to receive pharmacological standard of care treatment to treat their MDD (as determined by the treating physician(s) based on clinical judgement and local treatment guidelines) during the trial duration.
8. In the physician's opinion, acute psychiatric hospitalization is clinically warranted to treat the patient*s condition, and the patient is either already in the hospital or agrees to be hospitalized voluntarily for the required per protocol period.

Exclusion criteria

1. Any prior or current diagnosis of bipolar disorder, MDD with psychotic features, schizophrenia, or schizoaffective disorder as obtained from M.I.N.I.

at Screening
2. Patients with acute alcohol or substance use disorder or withdrawal symptoms requiring detoxification, or patients who went through detoxification treatment (inpatient or outpatient) within 1 month before Screening.
3. Participant has a current clinical diagnosis of autism, dementia, or intellectual disability
4. History of seizures. Note: childhood febrile seizures are not exclusionary
5. Participants with borderline personality disorder as obtained from M.I.N.I. at Screening.
6. Participants with suicidal ideation or behavior caused primarily by another non-MDD condition as obtained from M.I.N.I. at Screening
7.Known worsening or new appearance of suicidal ideation or behavior during a prior
treatment with ketamine or esketamine or within 2 months after last ketamine or esketamine
administration
8. Participants taking medications prohibited by the protocol
9. Intake of the following medications/ psychotherapy:
a. Esketamine or Ketamine 2 months before Screening
b. Monoamine oxidase inhibitors (MAOIs) 14 days before Screening
10. Any other condition (e.g. known liver disease/liver dysfunction, active malignancy, etc.) which in the opinion of the investigator would put the safety of the participant at risk, impede compliance or hinder completion of the study.

Study design

Design

Study phase:	2
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):	03-01-2022
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	23-03-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-05-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	13-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
Other	CMIJ821A12201
EudraCT	EUCTR2020-003720-16-NL
CCMO	NL75939.100.21