A Randomized, Open-label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared With Quetiapine Extended-Release in Adult and Elderly Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor

Published: 28-04-2020
Last updated: 25-03-2025

Primary objective:The primary objective of this study is to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine extended-release(XR), both in combination with a continuing selective serotonin reuptake inhibitor (...

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

Summary

ID

NL-OMON55043

Source
ToetsingOnline

Brief title
ESCAPE-TRD

Condition

- Mood disorders and disturbances NEC

Synonym
desolation, melancholy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Depression, Esketamine, Nasal Spray, Treatment-Resistant

Outcome measures

Primary outcome

Remission at the Week 8 visit, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of <=10.

Secondary outcome

- Remission at Week 8 visit (ie, MADRS total score of <=10 at the end of Week 8) and no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit.

Note: A relapse is defined by any of the following:

a) Worsening of depressive symptoms as indicated by MADRS total score >=22 confirmed by 1 additional assessment of MADRS total score >=22 within the next 5 to 15 days. The date of the second MADRS assessment will be used for the date

of relapse.

b) Any psychiatric hospitalization for

* worsening of depression

* suicide prevention or due to a suicide attempt

--> for any of these events, the start date of hospitalization will be used for the date of relapse.

c) Suicide attempt, completed suicide, or any other clinically relevant event determined per the investigator*s clinical judgment to be indicative of a relapse of depressive illness, but for which the participant was not hospitalized. The onset of the event will be used for the date of relapse. In case more than 1 of the relapse criteria are met, the earliest date will be defined as the date of relapse for that participant.

- Change from baseline at all visits for the following scale scores:

a) Clinician-rated MADRS:

* Overall severity of depressive illness (total score)

* Early onset of action (change in total score from baseline at Day 8 visit)

* Depressive symptoms (individual items)

b) Clinician-rated overall severity of depressive illness:

* Clinical Global Impression - Severity (CGI-S)

* Clinical Global Impression - Change (CGI-C), is a measure of change, analyzed as a score not as change from baseline

c) Participant-reported depressive symptoms: Patient Health Questionnaire 9-item (PHQ-9)

d) Participant-reported functional impairment and associated disability:

Sheehan Disability Scale (SDS)

e) Participant-reported health-related quality of life and health status:

36-item Short-Form Health Survey (SF-36)

f) Participant-reported Quality of Life in Depression Scale (QLDS)

g) Participant-reported European Quality of Life (EuroQoL) Group, 5-Dimension,

5-Level (EQ-5D-5L) questionnaire

h) Participant-reported work productivity: Work Productivity and Activity

Impairment (WPAI): Specific Health Problem (SHP) questionnaire

- Intervention-emergent adverse events (AEs), including intervention-emergent

AEs of special interest

Suicidal ideation and behavior: Columbia-Suicide Severity Rating Scale (C-SSRS)

Study description

Background summary

Depression is a major cause of morbidity and mortality, with global estimates of 300 million treated and untreated individuals worldwide. A depressive state with classical symptoms such as low (depressive/sad) mood, markedly diminished interest in activities, significant weight loss/gain, insomnia or hypersomnia, psychomotor agitation/retardation, excessive fatigue, inappropriate guilt, diminished concentration, and recurrent thoughts of death, persisting for more than 2 weeks is classified as major depressive disorder (MDD).
Ketamine affects fast excitatory glutamate transmission. Antidepressant (AD) effects may relate to increased brain-derived neurotrophic factor release and synaptogenesis. Esketamine, the S-enantiomer of ketamine, is approved and widely used for the induction and maintenance of anesthesia via intramuscular or intravenous (IV) administration. Because of the higher N-methyl-D-aspartate receptor affinity of esketamine over arketamine (R-enantiomer of ketamine), Janssen Research & Development is developing esketamine (not the racemate) for

AD therapy. Moreover, intranasal administration was investigated instead of IV administration, since intranasal administration can offer better convenience for patients and fewer errors in dosing, and esketamine can be rapidly and well absorbed via the intranasal route.

Study objective

Primary objective:
The primary objective of this study is to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine extended-release (XR), both in combination with a continuing selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI), in achieving remission in participants who have treatment-resistant MDD with a current moderate to severe depressive episode.

Secondary objective:
- To assess the efficacy of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in the proportion of participants being relapse-free at Week 32 after remission at Week 8.
- To assess the effect of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in:
* Clinician-rated overall severity of depressive illness
* Early onset of action
* Clinician-rated depressive symptoms
* Participant-reported depressive symptoms
* Participant-reported functional impairment and associated disability
* Participant-reported health-related quality of life and health status
* Participant-reported work productivity
- To assess the safety and tolerability of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI.

Study design

This is a randomized, open-label, rater-blinded, active-controlled, international, multicenter study to evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in participants 18 to 74 years of age, inclusive, with treatment-resistant MDD. A psychiatrist should determine eligibility of participants for inclusion in the study.

The study has 4 phases: an up-to-14-day screening phase, an 8-week acute phase, a 24-week maintenance phase, and a 2-week safety follow-up phase. During the acute phase, participants in the esketamine arm will have twice-weekly visits from Week 1 to Week 4 and once-weekly visits from Week 5 to Week 8; during the maintenance phase from Week 9 to Week 32, visits will be once weekly or every 2 weeks (even weeks) based on dosing. Participants in the comparator arm will

have weekly visits from Week 1 to Week 4, and then every 2 weeks for the remainder of the acute phase (Week 6 and Week 8) and the maintenance phase (Week 10, Week 12, etc) through Week 32. All participants have a safety follow-up
visit 2 weeks following the last dose of study intervention. Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for all follow-up visits through Week 32, according to the Schedule of Activities. The total duration of the study is approximately 36 weeks for all participants. The end of study is considered as the last visit for the last participant in the study.

A total of 622 participants will be randomly assigned on Day 1 (baseline) in a 1:1 ratio to 1 of 2 open-label study intervention arms (311 participants per arm). The randomization will be balanced by using randomly permuted blocks and will be stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]).

Intervention

Esketamine Arm: Participants will continue to take their current SSRI/SNRI in combination with esketamine nasal spray.
Comparator Arm: Participants will continue to take their current SSRI/SNRI which will be augmented with quetiapine XR as per the SmPC (or local equivalent, if applicable) starting on Day 1 and will continue through Week 32.

Study burden and risks

For the side effects of Esketamine and Quetiapine please consult the informed consent form.

For side effects of the tests:
- Blood draw: taking blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.
- ECG: There is generally no risk with having an ECG. The sticky patches used during the procedure may pull your skin or cause redness or itching.

Questionnaires: the completion of the questionnaires takes some time during the study visits.

Contacts

Public

Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL
Scientific
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:
1. male or female, 18 years (or older if the minimum legal age of consent in the country in which the study is taking place is >18 years) to 74 years of age, inclusive, at the time of signing the ICF.
2. at screening, each participant must meet DSM-5 diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the MINI.
3. at screening and baseline, each participant must have an IDS-C30 total score of >=34.
4.1 must be on a current antidepressive treatment that includes an SSRI/SNRI at screening that resulted in nonresponse (less than 25% improvement of symptoms) after having been given at an adequate dosage (based on antidepressive dosages from SmPC [or local equivalent, if applicable]) for an adequate duration of at least 6 weeks; however, at screening the participant must show signs of minimal clinical improvement to be eligible for the study.

Clinical improvement of a participant on their current AD treatment will be retrospectively evaluated in a qualified psychiatric interview performed by an experienced clinician.
At baseline (Day 1) prior to randomization, the investigator will evaluate any changes in the participant*s signs/symptoms of depression since the screening assessment and confirm that the inclusion criteria for the current AD treatment are still met (ie, nonresponse and minimal clinical improvement).
5.1 the current antidepressive treatment was immediately preceded by nonresponse to at least 1 but not more than 5 different consecutive treatments (all within the current moderate to severe antidepressive episode) with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks and must be documented (as described in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations: Source Documents) during screening.
6.1 must have been treated with at least 2 different antidepressive substance classes among the treatments taken at an adequate dosage for an adequate duration of at least 6 weeks resulting in nonresponse in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).
7. must be on a single oral SSRI/SNRI on Day 1 prior to randomization. Participants who are taking combination ADs and/or augmentation at screening are eligible for the study. All AD treatments, including any augmenting substances, must be stopped prior to randomization on Day 1 according to applicable SmPCs (or local equivalents, if applicable), except the SSRI/SNRI to be continued;
8. must be medically stable based on physical examination, medical history, vital signs (including blood pressure) at screening. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the participant*s source documents.
9. must be comfortable with self-administration of nasal medication and be able to follow the nasal administration instructions provided.
10. must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
11. must sign a separate ICF at baseline (Day 1) visit if he or she agrees to provide optional biomarker and/or genomic (DNA and RNA) samples for research (where local regulations permit). Refusal to give consent for the optional biomarker and/or genomic DNA and RNA research samples does not exclude a participant from participation in the main study.
12. a woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test prior to the first dose of study intervention on Day 1.
13. a woman must be
(a). Not of childbearing potential
(b). Of childbearing potential and practicing a highly effective, preferably userindependent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective

method while receiving study intervention and until at least 6 weeks after last dose -the end of relevant systemic exposure.
14.1 a man who is sexually active with a woman of childbearing potential during the study (ie, from Day 1 prior to first dosing) and for a minimum of 1 spermatogenesis cycle (defined as approximately 74 days) after receiving the last dose of study intervention (ie, esketamine nasal spray or quetiapine XR, both in combination with continuing SSRI/SNRI), must fulfill the following criteria:
(a). must be practicing a highly effective method of contraception with his female partner.
(b). must use a condom if his partner is pregnant.
(c). must agree not to donate sperm.
15. willing and able to adhere to the lifestyle restrictions specified in this protocol

Exclusion criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:
1. received treatment with esketamine or ketamine in the current moderate to severe depressive episode.
2. received treatment with quetiapine extended- or immediate-release in the current moderate to severe depressive episode of a dose higher than 50 mg/day.
3. had depressive symptoms in the current moderate to severe depressive episode that previously did not respond to an adequate course of treatment with electroconvulsive therapy (ECT), defined as at least 7 treatments with unilateral/bilateral ECT.
4. has no signs of clinical improvement at all or with a significant improvement on their current AD treatment that includes an SSRI/SNRI as determined at screening by an experienced clinician during the qualified psychiatric interview.
5. received vagal nerve stimulation or has received deep brain stimulation in the current episode of depression.
6.1 has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8 and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder
7. age at onset of first episode of MDD was >=55 years.
8. has homicidal ideation or intent, per the investigator*s clinical judgment; or has suicidal ideation with some intent to act within 1 month prior to screening, per the investigator*s clinical judgment; or based on the C-SSRS, corresponding to a response of *Yes* on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation

with specific plan and intent) for suicidal ideation, or a history of suicidal behavior within the past year prior to screening. Participants reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the acute phase should also be excluded.
9. history of moderate or severe substance use disorder or severe alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening or current clinical signs.
10. history (lifetime) of ketamine, PCP, lysergic acid diethylamide (LSD), or 3,4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder.
11. has a neurodegenerative disorder (eg, Alzheimer*s disease, vascular dementia, Parkinson*s disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment.
12. is currently suffering from seizures, has a history of epilepsy, Neuroleptic Malignant Syndrome, or Tardive Dyskinesia.
13.1 has one of the following cardiovascular-related conditions:
(a). cerebrovascular disease with a history of stroke or transient ischemic attack.
(b). aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
(c). history of intracerebral hemorrhage.
(d). coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before baseline (Day 1). Participants who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator*s clinical judgment, can be included.
(e). uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability.
(f). hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
(g).confirmed or suspected cardiomyopathy or myocarditis
(h). New York Heart Association Class III-IV heart failure of any etiology.
14. has clinically significant or unstable respiratory conditions, including, but not limited to:
(a). significant pulmonary insufficiency, including chronic obstructive pulmonary disease.
(b). sleep apnea with morbid obesity (body mass index >=35).
15. uncontrolled hypertension despite diet, exercise, or antihypertensive therapy on Day 1 or any history of hypertensive crisis or ongoing evidence of uncontrolled hypertension defined as a supine SBP >140 mmHg or DBP >90 mmHg.
Potential participants may have their current antihypertensive medication(s) adjusted during the screening phase and be re-evaluated to assess their blood pressure control prior to randomization.
16. history of additional risk factors for torsade des pointes (eg, heart failure, hypokalemia, or family history of long QT syndrome).
17. history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) or alanine

aminotransferase (ALT) or aspartate aminotransferase (AST) values >=3 × the upper limit of normal in routine laboratory test or medical record or at screening.
18. has a fasting triglyceride concentration >=500 mg/dL at screening.

Refer the protocol for all the exclusion criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	26-10-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Seroquel
Generic name:	Quetiapine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Spravato
Generic name:	Esketamine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-07-2021
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	EUCTR2019-002992-33-NL
CCMO	NL73300.056.20

Study results

Date completed: 13-06-2022

Results posted: 14-07-2023

First publication
22-06-2023

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

Internal documents
File