Intranasal Esketamine Against Depression. A real world clinical treatment Cohort-Study in the Netherlands (INESKAD)

First published: 05/01/2026

Last updated: 05/01/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000892

Study ID

1000000892

DARWIN EU® study

No

Study countries

Netherlands

Study description

Rationale: Intranasal esketamine is a new antidepressant drug with an alternative mechanism of action than routinely used antidepressants. Experience with esketamine especially in more severely treatment resistant depressed (TRD) patients is limited but needed in terms of real-world effectiveness and acceptability.
Objective: To collect and pool pseudoanonymised short- and long-term effectiveness and acceptability data for the treatment with intranasal esketamine in TRD-patients treated across all esketamine treatment centres in the Netherlands.

Study design: unblinded, naturalistic cohort study of patients who are treated with intranasal esketamine.
Study population: All patients with treatment resistant depression (TRD; defined as non-responsive to ≥2 antidepressant trials used at adequate dosages for ≥6 weeks), aged ≥18 years, clinically eligible for treatment with esketamine nasal spray.

Intervention: Open-label esketamine intranasal spray at 28-84mg/session twice weekly for 4 weeks (as addition to an antidepressant). Treatment responders will enter a Continuation (maintenance) Phase with 4 weeks weekly and thereafter -if possible- lower frequency of administration.

Main study parameters/endpoints: Primary outcome: change in MADRS-score relative to baseline. Secondary outcomes: change in IDS-SR-score relative to baseline; Quality of life and Daily functioning, adverse effects (KSET), cost-effectiveness and treatment discontinuations. We will measure behaviour on the Pavlovian instrumental transfer (PIT) task before and after 4 weeks of treatment.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: as a potential alternative treatment for TRD, patients

might benefit from this treatment. As long as the manufacturer’s precautions are followed there is minimal risk involved in this treatment. In this project no additional interventions or extra measurements will be performed apart from clinical assessments and

Study status

Ongoing

Research institutions and networks

Institutions

Radboud university medical center (Radboudumc)

Netherlands

First published: 30/06/2022

Last updated: 21/03/2025

Institution | **Educational Institution** | **Hospital/Clinic/Other health care facility** | **ENCePP partner**

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Amsterdam UMC

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

Leiden University Medical Centre (LUMC)

First published: 01/02/2024

Last updated: 01/02/2024

Institution

GGZ Drenthe, ApareeGGZ, UMCG, Elisabeth Tweesteden Ziekenhuis, Maxima Medisch Centrum Eindhoven, Mondriaan / PsyQ Maastricht, GGZ Delfland, Antonius ziekenhuis Nieuwegein, Parnassia Psy-Q Den Haag, Parnassia Antes, Parnassia Noord-Holland Castricum, Synaeda/GGZ Friesland, Vincent van Gogh, ProPersona, GGNet,

GGZ Centraal, Reinier v Arkel, Amphia, Emergis, Rivierduinen, GGZ Noord-Holland Noord, Lentis, Spaarne gasthuis, Altrecht, Isala, Rivierenland, Ziekenhuis Groep Twente, Gelre Ziekenhuis, GGz InGeest

Networks

Esketamine Nasal spray Consortium - Netherlands (ENC-NL)

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed
Actual: 01/01/2020

Study start date
Actual: 01/01/2020

Date of final study report
Planned: 31/12/2030

Sources of funding

- Other

More details on funding

ENC-NL has been funded through in-kind contributions of participating centers regarding their staff to participate in the consortium/Network.
ENC-NL has received support from J&J by two unrestricted Educational Grants (July 2023-2024 and 2025-2026).

Study protocol

C1. research-protocol INESKAD v2.3 clean.pdf (992.02 KB)

C1. research-protocol INESKAD v2.4 clean.pdf (990.51 KB)
C1. research-protocol INESKAD v2.4 clean.pdf (990.51 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Other study registration identification numbers and links

Link to ENC-NL website (in Dutch)

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study topic, other:

Treatment Resistant Depression

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Drug utilisation

Effectiveness study (incl. comparative)

Evaluation of patient-reported outcomes

Other

Safety study (incl. comparative)

If ‘other’, further details on the scope of the study

Prestratification

Data collection methods:

Primary data collection

Study design:

This is a cohort study of patients who are treated with intranasal esketamine (open label). For the objectives of this study, no other routines will be applied apart from the necessary measurements in clinical medical records of the patients, who will provide informed consent for the data-collection

Main study objective:

Primary Objective: To collect short- and long-term effectiveness and acceptability data for the treatment with intranasal esketamine in treatment resistant depressed patients treated in collaborating esketamine treatment centres.

Secondary Objective(s):

To pool pseudoanonymised data of effectiveness and acceptability of esketamine intranasal from based on clinical registrations in patient’s real-world health records.

To use predicted treatment response based on pooled clinical and behavioural data as pre-selection tool.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

ESKETAMINE

Anatomical Therapeutic Chemical (ATC) code

(N06AX27) esketamine

esketamine

Medical condition to be studied

Depression

Additional medical condition(s)

Treatment Resistant Depression

Population studied

Short description of the study population

In order to be eligible to participate in this study, a subject must meet the following

Inclusion criteria:

- Clinical diagnosis of primary MDD, preferably confirmed by a structured clinical interview (MINI/SCID-I)
- Treatment Resistant Depression, defined as non-response to at least two antidepressants used at adequate dosages for a minimum of 6 weeks

- Age >18 years old (no maximum age)
- Current use of (and compliance to) an antidepressant (non-SSRI/SNRI is allowed)

Exclusion criteria:
- Current psychotic illness
- Bipolar disorder
- Severe suicidal/homicidal risk (to be determined by psychiatrist)
- Insufficient understanding of Dutch to fill-out questionnaires and/or understand information
- Unable to self-administer esketamine nasal spray
- History of moderate-severe substance abuse or dependence meeting DSM-5 criteria
- Pregnancy or wish to become pregnant
- No form of adequate anti-conception (both genders)
- Instable epileptic disease/seizures in previous 6 months
- Unstable hypertension (>140/90 mmHg) or recent cardiovascular event (cerebrovascular, myocardial, aneurysmal vascular disease, angina-pectoris, . hemodynamically significant valvular heart disease, NYHA Class III-IV heart failure)
- Hypo-thyroidism, liver-failure/cirrhosis
- Any anatomical or medical condition that may impede delivery or absorption of intranasal esketamine
- Other unstable somatic/medical illness
- Previous non-response to esketamine (intranasal) or ketamine in current MDD episode
- Known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine and/or its excipients

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Special population of interest, other

Treatment Resistant Depression

Estimated number of subjects

10000

Study design details

Setting

Primarily outpatients treated in day-care facilities due to EMA-regulatons, sometimes inpatients if disease severity requires hospitalisation.

Comparators

None

Outcomes

Primary endpoint is the change (relative to baseline) in clinician-rated MADRS score (Montgomery 1979) at 4 and 8 weeks of treatment.

Secondary endpoints are:

- The change (relative to baseline) in clinician-rated MADRS score (Montgomery 1979) over time measured in 4 weeks intervals after week 8.
- The change (relative to baseline) in self-rated IDS-SR score (Rush 1996; Trivedi 2004) at 4 weeks and over time measured in 4 week intervals thereafter.
- Quality of Life measurement (EQ-5D-5L) at 4 weeks and over time measured in 4 week intervals thereafter (relative to baseline)
- Level of functioning at 4 weeks (WHODAS-2.0) and over time measured in 4 week intervals thereafter (relative to baseline)
- Cost-effectiveness (modified TiC-P) at 4 and 8 weeks and 3 monthly intervals thereafter (relative to baseline)
- The change in mood (before-after) esketamine intranasal spray per session as measured by a visual analogue scale before administration and after completion of the session (before leaving).
- Occurrence of adverse effects including dissociative symptoms at T=40 min after administration (or as close as possible) and at the end of the session as measured with the K-SET per session
- Discontinuation rates: due to adverse effects of the treatment or other reasons.
- Changes in blood-pressure during esketamine intranasal sessions (baseline, 10, 40, 90 minutes per session)
- Follow-up 3 months after discontinuation of intranasal esketamine treatment.
- With the PIT, we apply a test that quantifies affect-driven avoidance and approach behaviors, with great potential in predicting the effect of intranasal esketamine on TRD (baseline, 4 wekes of treatment).

Before the treatment is initiated we will assess the level of treatment resistance with the DM-TRD

Data analysis plan

For the continuous MADRS-scores differences relative to baseline will be expressed over time. This will initially be done for the full sample. Subsequently we will investigate the association of the primary outcome with the level of treatment resistance and specific aspects thereof (e.g. ECT-non-responders) with linear mixed models (to accommodate repeated follow-up measurements and unavoidable missing data over time). We will pool this data across different treatment centres in order to increase power and obtain more quantitative information about possible characteristics of responders vs non-responders.
For secondary outcome study parameters (IDS-SR, QoL and level of functioning) we will use a comparable approach as for the primary study outcome.
Discontinuation rates will be described over time, also in relation with level of TRD. The DM-TRD will be used as a continuous variable in regression and mixed model analyses. For illustrative purposes the scores of this scale can be split into tertiles (low and high levels of TRD).
Occurrence of dissociative symptoms and blood-pressure per session will be examined for stability over time. Moreover, the severity of these adverse effects and the variation thereof between patients will be described descriptively.

For each separate analysis done in this consortium, we will pre-register an analysis plan at the Open Science Framework (https://osf.io/)

Summary results

To be expected

Documents

Link to the consortium agreement ENC-NL

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Patient treatment information from the (electronic) Health Records

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Data sources (types)

Drug prescriptions

Electronic healthcare records (EHR)

Non-interventional study

Patient surveys

Spontaneous reports of suspected adverse drug reactions

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Not applicable

Procedures

Procedure of data extraction

20251001_INESKAD Veldgids_V1.7.pdf

English (13.08 MB - PDF) View document

Lin k to Google-Drive with data collection procedures