TEMPLATE RESEARCH PROTOCOL

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

PROTOCOL TITLE '**Intra-Nasal Esketamine Against Depression. A real world clinical treatment Cohort-Study in the Netherlands (INESKAD)**'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
PIT	**Palvovian to instrumental transfer**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

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 and should be quantified more in terms of effectiveness and acceptability.
Objective: (1) To collect pseudo-anonymised short- and long-term effectiveness and acceptability data for the treatment with esketamine intranasal in TRD-patients treated in collaborating esketamine treatment centres in the Netherlands. (2) To pool pseudoanonymised data of effectiveness and acceptability of esketamine intranasal based on clinical registrations in patient's real-world health records. (3) To use predicted treatment response based on pooled clinical and behavioural data as pre-selection tool.
Study design: unblinded 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.
Study population: 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, treatment discontinuations and behaviour on the Pavlovian instrumental transfer (PIT) task.
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 and instructions are followed there is a minimal risk involved in this treatment. In this project no additional interventions or extra measurements will be performed apart from clinically relevant assessments for routine health care, except for the PIT task. We therefore request for a non-WMO statement.

INTRODUCTION AND RATIONALE

Treating Major Depressive Disorder (MDD) is a health care challenge of paramount importance worldwide, as the disease is the leading cause of disability worldwide, impairs overall health, social functioning, productivity and reducing life expectancy with 10 years (Walker 2015; Sobocki 2006; Mathers 2006). About one-third of patients with MDD fail to achieve remission despite treatment with multiple antidepressants, hence have treatment-resistant depression (TRD) (Fava 2003). In patients who respond, time to onset of effect is typically 3 to 7 weeks, during which time patients remain symptomatic and at risk of self-harm (Rush 2006). There is an unmet need to develop novel treatment providing an effective, rapid-acting and sustained relief of depressive symptoms.
Research on mood disorder pathophysiology has implicated abnormalities in glutamatergic transmission (Sanacora 2012; Duman 2019). Ketamine is a noncompetitive antagonist of glutamate receptors of the N-methyl-D-aspartate (NMDA) type, which can make fast excitatory glutamate transmission happen, increase the release of brain-derived neurothrophic factor and stimulate synaptogenesis, with mood-elevating effects occurring as rapid as within several hours (Kavalali 2012). Esketamine, the s-enantiomer of ketamine, which has a higher affinity for the NMDA receptor than the r-enantiomer, has recently been approved in the United States as a nasal spray for treatment resistant depression (TRD). The efficacy and safety of esketamine for TRD were evaluated in three 4-week, placebo controlled, parallel-group studies with (two studies including adults 18 to 65 years of age (total of 197+297=494 patients), and one in patients of 65 years and above (n=138)) and one longer-term randomized withdrawal study. The long-term safety was evaluated in a 12-months open-label safety study. In summary, Phase II and III studies with esketamine in n=632 patients, demonstrated rapid onset and persistent efficacy of intranasal esketamine administered adjunctive to an ineffective oral antidepressant, compared to placebo nasal spray in patients with TRD (Singh 2016; Daly 2018; Popova 2019; Fedgchin 2019). In addition, there is evidence of sustained benefit over a variable time with a maximum of 92 weeks in a phase III long-term maintenance study (Daly 2019). Despite this evidence, relatively few studies have been performed on esketamine, and even less in “real world” TRD patients with chronic and often more severely treatment resistant depression. Moreover, the patient characteristics of those who respond versus those who remain symptomatic after treatment with intranasal esketamine remain unclear.
Since December 18th 2019, esketamine intranasal obtained a European marketing authorization from EMEA. Thereafter, the manufacturer issued a compassionate use program (CUP) for the Netherlands before the reimbursement would be established, aiming at severely treatment resistant depressed patients (e.g. unsuccessful response to MAO-Inhibitors and/or ECT). As treatment with esketamine intranasal requires protocolized administration under strict supervision of patients in at least a day-care treatment facility, a limited number of centres will provide esketamine treatment, initially via the CUP, which, after reimbursement, was continued with new treatment centres. Current centres where esketamine intranasal spray treatments are administered: Radboudumc, Amsterdam UMC, UMC Utrecht, LUMC, 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. These centres are collaborating on exchanging treatment protocols and clinical experience in order to increase the knowledge with this new application.

OBJECTIVES

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

Secondary Objective(s):

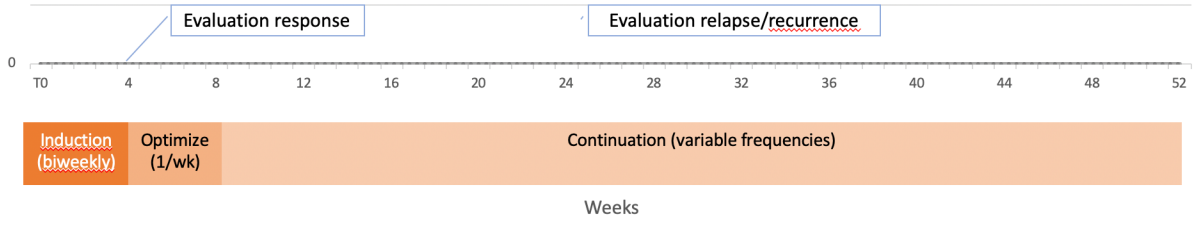
To pool pseudoanonymised data of effectiveness and acceptability of esketamine intranasal from based on clinical registrations in patient's real-world health records.

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

1. STUDY DESIGN

This is an unblinded cohort study of patients who are treated with intranasal esketamine (open label). This cohort is a cohort study of real world regular treatment with esketamine intranasal administration. For the objectives of this study, no other routines or interventions will be applied apart from the necessary measurements used for optimal clinical care and decisions about effectiveness and acceptability, except for the PIT task. All data, except for the PIT task, can be obtained from the clinical medical records of the patients, who will provide informed consent for the data-collection as described in this protocol. Data from the PIT task will be collected via online testing using Gorilla (cf. 'Online testing' covered under CMO2014/288).

Figure 1.



2. STUDY POPULATION

2.1 Population (base)

Depressed patients with TRD, referred to the hospital for treatment of their MDD.

2.2 Inclusion criteria

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

2.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- 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

2.4 Sample size calculation

As this is a cohort study, in which we want to use clinical data for summary purposes regarding effectiveness and acceptability, we did not perform an a priori power calculation.

3. TREATMENT OF SUBJECTS

Although this is a non-interventional cohort study of routine medical treatment, we will here describe the esketamine intranasal treatment schedule.

3.1 Investigational product/treatment

Treatment will be provided according to the 'TREATMENT GUIDELINES for Esketamine Nasal Spray for the use of treating Physicians' as provided by the manufacturer.
In brief, treatment will be provided initially twice per week during the Induction Phase, followed by a Continuation (maintenance) Phase, where in week 5-8 treatment will be provided once weekly and from week 9 onwards dosing can be tried to be reduced to once every two weeks (Figure 1). Usual initial dosages are 56mg/session, which may be increased to 84mg/session. Especially in elderly the initial starting dose will be lower (28mg/session), and if responsive, patients may stay on that dosage. Dosing frequency will be individualized to the lowest frequency to maintain remission/response. At the end of Induction Phase, evidence of therapeutic benefit (based on the clinician's evaluation of symptomatic change and/or improvement in functioning or quality of life) will be evaluated to determine need for continued treatment in the Continuation (maintenance) Phase. After depressive symptoms improve, treatment is recommended for at least 6 months.

Each treatment session consists of administration of esketamine nasal spray and post-administration observation under the supervision of a healthcare professional. Patients will administer the nasal spray themselves. Because of possible nausea and vomiting after administration of esketamine nasal spray, patients should not eat for at least 2 hours before administration and not to drink liquids at least 30 minutes prior to administration. Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medications within 1 hour before administration of esketamine nasal spray.
All patients remain at the clinical site until safety procedures have been completed (monitoring of blood pressure and dissociative symptoms) and the patient is ready for discharge. Readiness to leave is assessed based on clinical judgement of dissociative symptoms measured 40 minutes after the last dose administered or as soon as possible after the patient wakes up. Patients must not drive a car or work with machines for 24 hours after esketamine dosing, therefore patients need to have transportation home after the procedure.

3.2 Use of co-intervention (if applicable)

Patients will continue their antidepressant medication (SSRI, SNRI, TCA), which might be optimized according to dosage or therapeutic drug monitoring (if appropriate).
If possible, a maximum of 3 mg lorazepam (or equivalents) daily is used, and preferably stopped during the treatment.

3.3 Escape medication (if applicable)

N/A; this is left to the judgement of the clinician

4. INVESTIGATIONAL PRODUCT

4.1 Name and description of investigational product(s)

Esketamine intranasal (Spravato).

4.2 Summary of findings from non-clinical studies

See SPC of Spravato 28mg nasal spray at
https://www.medicines.org.uk/emc/product/10977/smpc#gref

4.3 Summary of findings from clinical studies

See SPC of Spravato 28mg nasal spray at
https://www.medicines.org.uk/emc/product/10977/smpc#gref

4.4 Summary of known and potential risks and benefits

See SPC of Spravato 28mg nasal spray at
https://www.medicines.org.uk/emc/product/10977/smpc#gref

4.5 Description and justification of route of administration and dosage

Nasal spray administration of esketamine has approximately 50% bioavailability compared to i.v. administration, while oral administration reduces bioavailability to approximately 8-18.6% (Andrade 2015; 2017; Janssen 2019; Perez-Ruixio 2020.

4.6 Dosages, dosage modifications and method of administration

Esketamine treatment will be provided via nasal spray. Each device contains 28 mg of esketamine, which is 2 sprays, one for each nostril. It is intended for administration by the patient under the supervision of a healthcare professional. In elderly (age ≥65 years) the starting dose will be 28 mg, in younger adults the starting dose will be 56 mg (2 devices). If adverse effects are tolerable, the next session the dose will be increased to a maximum of 84 mg/session (i.e. 3 devices). To prevent loss of medication, the device should not be primed before use.

4.7 Preparation and labelling of Investigational Medicinal Product

The product will be obtained from Janssen Inc. either via the CUP or after reimbursement is established via the hospital pharmacy. Labelling will be done according to GMP.

4.8 Drug accountability

N/A Routine delivery of drug via pharmacy.

5. NON-INVESTIGATIONAL PRODUCT

N/A

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

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

6.1.2 Secondary study parameters/endpoints

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; Janssen 2013) at 4 weeks and over time measured in 4 week intervals thereafter (relative to baseline)
- Level of functioning at 4 weeks (WHODAS-2.0; Forero 2018) 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 KSET (Short 2020) 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)
- Follow-up 3 months after discontinuation of intranasal esketamine treatment.

6.1.3 Other study parameters (if applicable)

Before the treatment is initiated we will assess the level of treatment resistance with the DM-TRD (Peeters 2016; Ruhe 2012).

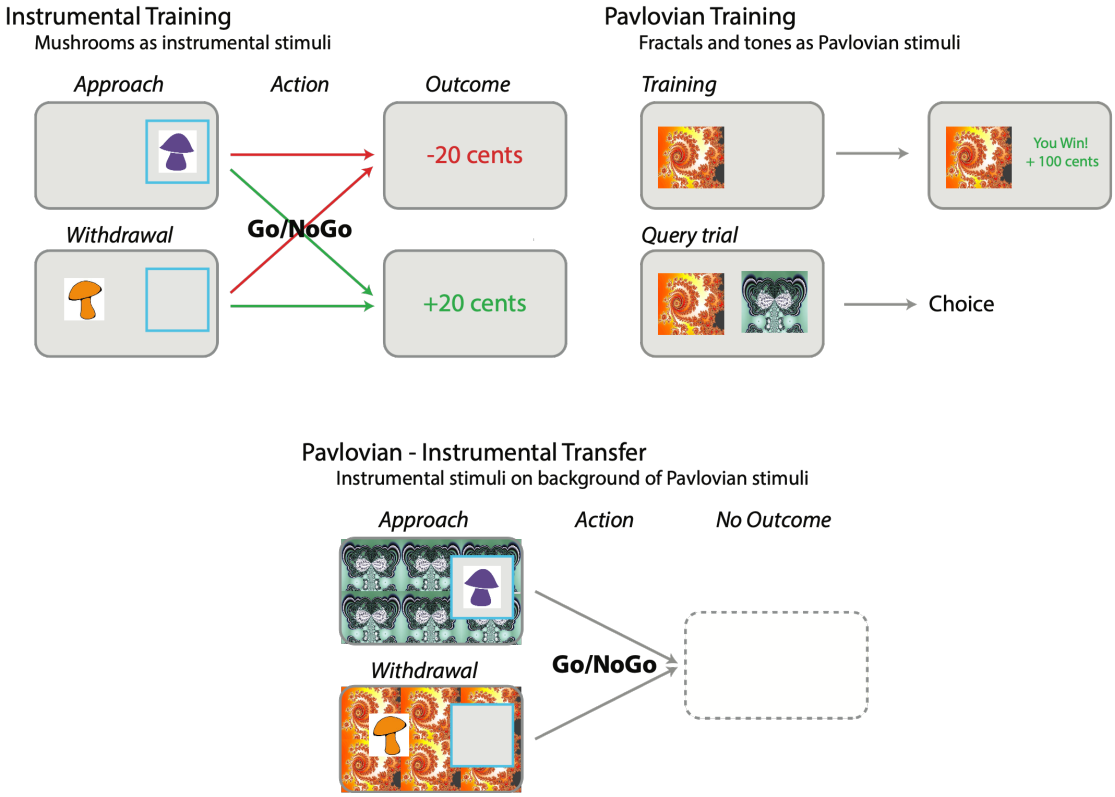


Figure 2. Outline of the Pavlovian to instrumental transfer (PIT) task - **Instrumental training.** To centre the cursor, participants click in a central square. The experiment consists of a first block with exclusively instrumental approach trials (n=120) and a second block with exclusively withdrawal trials (n=120). In approach trials (top), participants chose whether to move the cursor towards the mushroom and click inside the blue frame onto the mushroom (go), or do nothing (nogo). In withdrawal trials, they instead move the cursor away from the mushroom and clicked in the empty blue frame (go) or do nothing (nogo). Outcomes are presented immediately after go actions, or after 1.5 seconds. Per block there are 3 "good" and 3 "bad" instrumental stimuli. Participants play each block once per testing day. Instrumental stimuli are different for both blocks and both days. **Pavlovian training.** Participants passively view stimuli and hear auditory tones, followed by wins and losses. There are five fractal/tone combinations. Each combination is displayed 12 times in the first block and another 6 times in the second block. **Pavlovian-instrumental transfer.** Participants respond to the instrumental stimuli trained during the instrumental training stage, with Pavlovian stimuli tiling the background. No outcomes are presented, but participants are instructed that their choices count towards the final total. No explicit instructions about the contribution of Pavlovian stimuli towards the final total are given.

2. Pavlovian to Instrumental Transfer Task

In this task (see Figure 2) we assess to what degree instrumental behavior of participants is influenced by previously learned Pavlovian stimuli-outcome associations. To do this, we first train subjects to react to instrumental stimuli (IS) to earn money. In this phase, participants are asked to approach the stimuli with positive outcome by clicking on them. Next, we show subjects neutral pictures that we then associate with monetary wins and losses. By this latter classical (or Pavlovian) conditioning procedure these neutral pictures acquire an affective valence and become conditioned stimuli (CS) with appetitive and negative valence respectively. Then we ask subjects to react to the IS again, but now also show them the CS. Afterwards, the participants are again trained to react to instrumental stimuli, but now the participants need to make withdrawal responses, where they need to click on the stimuli to put them away and where they "collect" the stimuli when they do not respond. Again, this is followed by the task where the IS and CS are shown together

and participants need to respond to the IS in the learned manner. Previously we have shown, that these CSs can invigorate or inhibit behavior dependent on the valence of the CS (appetitive vs. negative): for example, the appetitive CS promotes and the negative CS inhibits approach actions (Geurts, Huys, den Ouden, et al., 2013; Huys et al., 2011).

Hypothesis:
We aim to deliver a prediction model that relates closely to the mechanisms underlying TRD and to the mode of action of s-ketamine for which PIT is the foremost candidate. First, s-ketamine indirectly influences ascending monoaminergic pathways via neural firing in the brain's 'anti-reward center', the lateral habenula. Second, these monoaminergic pathways are implicated in using emotional information to guide goal-directed behavior. Disturbances in this behavioral guidance are key to the negative self-reinforcing mechanisms found in TRD: e.g. increased avoidance and blunted approach behavior in resp. negative and positive contexts. Thus, a test that quantifies affect-driven avoidance and approach behaviors would carry great potential in predicting the effect of s-ketamine on TRD. The Pavlovian to instrumental transfer test (PIT), is exactly the right test, which indeed has been shown to predict recovery of depression (Huys, 2016) and is widely used in psychiatric disorders (see for review Garbusow, 2022). Moreover, it quantifies guidance of avoidance and approach behaviors by affective information, which has been related to depression (Huys 2016, Nord, 2018, Geurts 2023a *in preparation*) and is dependent on monoaminergic signaling (Geurts 2013, Geurts 2023b *in preparation*). Thus, we hypothesize that this test, in conjunction with conventional, clinical predictors, can help us stratify and predict individual treatment effects, thus advancing clinically applicable precision psychiatry.

6.2 Randomisation, blinding and treatment allocation

N/A

6.3 Study procedures

All procedures are part of routine clinical practice. No invasive or additional measurements will be done.

Initial assessment for eligibility for esketamine intranasal treatment consists of:

- Assessment of in- and exclusion criteria including determination of DSM-5 diagnosis by either clinical or semi-structured clinical interview.
- Level of treatment resistance (DM-TRD)
- Drug and alcohol screening (if appropriate)
- Pregnancy test (if appropriate)
- Routine ECG and laboratory assessment
- Assessment of baseline MADRS and IDS-SR score

- Internet-based delivery of PIT test via GDPR certified online testing platform Gorilla

After inclusion, patients will continue the antidepressant they are currently using. This treatment might be optimized according to dosing or TDM. Patients start treatment in accordance with the schedule provided by the manufacturer and described under 4.1 (Figure 1).

Every session:
- VAS-ratings of mood will be asked at every session before-after esketamine administration
- Adverse effects including dissociation at 40 minutes after the last dose of esketamine, or – in case of more pronounced dissociation- as close as possible and at the end of the session (KSET)

During the Induction Phase weekly assessments of effectiveness will be done. In the Continuation (maintenance) Phase this will be continued every second week at frequencies of administration ≥1/week, while if the frequency is ≤1/2 weeks, assessments will be done monthly for the first 2 months, followed by every two months thereafter:
- Repeated assessments of MADRS and IDS-SR scores.

Formal evaluations of the treatment will be performed at regular intervals according to clinical judgement. The first evaluation of effectiveness will be after 4 weeks of twice weekly administration. This will also be the second and last time that the subject is asked to do the online PIT test.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4.1 Specific criteria for withdrawal

- Intolerance of esketamine intranasal treatment
- Non-response to the treatment after 4 weeks

6.5 Replacement of individual subjects after withdrawal

N/A

6.6 Follow-up of subjects withdrawn from treatment

N/A

6.7 Premature termination of the study

N/A

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

N/A

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to esketamine treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the manufaturer and Lareb without undue delay after obtaining knowledge of the events.

7.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;

3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC <*reporting via webportalToetsingOnline is only applicable for investigator initiated studies*>:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

7.3 Annual safety report

N/A

7.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

7.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

N/A

8. STATISTICAL ANALYSIS

8.1 Primary study parameter(s)

For the continuous MADRS-scores differences relative to baseline will be used 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).

For the second aim of the project, we aim to 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.

8.2 Secondary study parameter(s)

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.

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 the second aim of the project, we aim to 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.

8.3 Other study parameters

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 medium and high levels of TRD).

PIT and clinical data will be combined and used to (iteratively) train machine learning algorithms, to build an optimal prediction tool for clinical decision-making: Therefore, we adopt a computational psychiatry approach, a rising field fueled by the lack of break-throughs in psychiatric practice and inspired by advances in cognitive neuroscience and data-science. Computational psychiatry aims to improve clinical practice through mechanism- and machine-learning based predictions. Accordingly, we will use advances in computational cognitive neuroscience (PIT) and machine-learning (prediction) towards improved outcomes for TRD patients. This is timely because of evidence of clinical predictive value of PIT (Huys, 2016, Chen 2020), iSk registration for TRD and the availability of solid computational frameworks with readily employable machine-learning

algorithms, which enable us to perform predictions on the individual level within high-dimensional data.

Following the STROBE22 guideline, we will build a model to predict response in terms of depressive symptom reduction after 4 weeks of treatment with esketamine intranasal sprays. Clinical and computational parameters from PIT (easy to administer, web-based test measuring the influence of affect on reward-driven behaviors), collected before treatment initiation in 350 TRD patients, will be used as predictors. To predict response based on multiple predictors (PIT, questionnaire, demographical, clinical data) I will follow TRIPOD(-AI) guidelines and use common machine learning procedures (i.a. support vector machine, penalized regression and tree-based approaches) with cross-validation to prevent overfitting. The best algorithm in terms of precision-recall area under the curve will be tested on a hold-out test dataset (not involved in algorithm tuning) against at least reasonable specificity (90%) for non-response, making it acceptable for clinical purposes. As external validity is very important (and often not taken into account) in translational research, we will test algorithms again through continuous data collection and assess clinical utility with common test-statistics. Test data will be used to optimize algorithms iteratively, by further hyperparameter tuning (test and tune procedure).

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

8.4 Interim analysis

N/A

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

N/A

9.2 Recruitment and consent

Recruitment of the project will be via the regular referrals to the Radboudumc Department of Psychiatry, which has a role as referral centre for TRD, or other participating centres. Possibility of esketamine intranasal treatment will be communicated with colleagues and our network.

To all patients the purpose of this data collection will be explained with both written and oral information and informed consent for data collection and (pseudo-anonymised) pooling will be obtained and stored.

9.3 Objection by minors or incapacitated subjects (if applicable)

N/A

9.4 Benefits and risks assessment, group relatedness

N/A. Treatment and assessment of risk and benefits will be done from a clinical/treatment perspective.

9.5 Compensation for injury

N/A

9.6 Incentives (if applicable)

N/A

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All data (questionnaires and evaluations) will be primarily recorded in the patient's health record. Only after informed consent data will be abstracted and anonymised by a study-number. For the second aim of this project the study-number will only disclose the treating hospital where the patient was treated, no referral to initials or birth-date of participants will be made in the study-number. The key between the study-number and the patient will be stored at the hospital (at a secured directory only accessible to the local physician) and will not be shared outside the hospital.

10.2 Monitoring and Quality Assurance

N/A

10.3 Amendments

Current versions 2.3 and 2.4 contains amendments.

10.4 Annual progress report

N/A

10.5 Temporary halt and (prematurely) end of study report

N/A

10.6 Public disclosure and publication policy

Summary reports for the hospital and internal evaluations will be made. For the second aim of this project we will aim to publish a case-series/cohort-report of patients treated with intranasal esketamine and explore effectiveness and acceptability of this new treatment in relation to the level of TRD when the treatment was initiated.

11. STRUCTURED RISK ANALYSIS

<This chapter is applicable for research with any product: medicinal product, food product, medical device or other (as described in chapter 6 and 7)>

11.1 Potential issues of concern

< In this final paragraph of the research protocol a structured risk analysis which consists of a number of steps is required. The analysis should result in a comprehensive overall synthesis of the direct risks for the research subjects in this study in chapter 13.2. The risk considerations on the various issues listed below should be supported by up to date information and should be clearly described to allow a thorough review by the METC. For details one may refer to the previous chapters, the Investigator's Brochure (IB) or a similar document (if applicable), peer reviewed papers in (biomedical/scientific) journals. The issues below are provided to structure your considerations and allows an efficient communication with the METC when questions arise as a result of the review of your research protocol. The remarks per item are provided as a guidance for describing your considerations. Should issues not be applicable, please indicate so.
*For registered products to be used within the indication and **not** in combination with other products chapter 13.1 can be skipped; explain in chapter 13.2 why 13.1 is skipped >*

a. Level of knowledge about mechanism of action
Esketamine is an N-methyl-D-aspartate (NMDA) antagonist; the mechanism of action putatively results from noncompetitive binding to these NMDA glutamate receptors. Esketamine has a threefold to fourfold higher affinity for NMDA receptors than arketamine.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
See SPC of Spravato 28mg nasal spray at https://www.medicines.org.uk/emc/product/10977/smpc#gref

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
Yes.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Yes

e. Analysis of potential effect
See SPC of Spravato 28mg nasal spray at https://www.medicines.org.uk/emc/product/10977/smpc#gref

f. Pharmacokinetic considerations

See SPC of Spravato 28mg nasal spray at
https://www.medicines.org.uk/emc/product/10977/smpc#gref

g. Study population
Patients with TRD.

h. Interaction with other products
See SPC of Spravato 28mg nasal spray at
https://www.medicines.org.uk/emc/product/10977/smpc#gref

i. Predictability of effect
Not available yet

j. Can effects be managed?
Yes

11.2 Synthesis

Use of esketamine intranasal has been studied quite extensively already in TRD-patients and frequencies of adverse effects are moderate, especially during administration dissociative symptoms and increases of blood-pressure might occur which are variable between patients and self-limiting. Pharmacokinetics of esketamine are well known. As long as the manufacturer's precautions and instructions are followed there is a minimal risk involved in this treatment.

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