STATISTICAL ANALYSIS PLAN

Safety Effect Moderators of Intranasal Esketamine used in Assocation with a SSRI or SNRI: An Individual Participant Data Meta-Analysis

Statistical Analysis Plan: Version 1

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Study Drug: Esketamine Nasal Spray

TEAM - 1:
Cora Burgwinkel, Florian Naudet, Ka Hin Tai,
Mian Haider Ali, Tobechi Obinwanne, Ulrike Held

List of Abbreviations and Definitions

TERM	Abbreviation / Definition
FDA	Food and Drug Administration
IPD	Individual Participant Data
IPDMA	Individual Participant Data Meta-analysis
OSF	Open Science Framework
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TEAE	Treatment-emergent Adverse Event
TRD	Treatment-resistant Depression
YODA	Yale University Open Data Access

1 Objective

While previous individual participant data meta-analyses (IPDMAs) have examined baseline clinical and demographic characteristics as moderators of esketamine efficacy, important gaps remain regarding whether treatment-emergent adverse events (TEAE) differ across patient subgroups (e.g., by age or sex). Evaluating potential effect moderators for safety outcomes is clinically important, as conventional aggregate safety reporting does not adequately capture individual-level heterogeneity in adverse event profiles or the clustering of therapeutic benefit and acute tolerability (Jones et al. 2022; Ochs-Ross et al. 2022). Our objective is to assess the subgroup-specific safety of intranasal esketamine using individual participant data (IPD).

2 Study Methods

2.1 Design

An IPDMA derived from double-blind, randomised, placebo-controlled trials of esketamine in association with a selective serotonin reuptake inhibitor (SSRI) or a serotonin and norepinephrine reuptake inhibitor (SNRI) in patients with depression.

2.2 Participants, Interventions, Comparators, Outcomes, and Study Design (PICOS)

2.2.1 Participants

Studies that include esketamine naive participants with treatment resistant depression (TRD). Participants must be 18 years or older.

TRD refers to a depressive episode with inadequate response to at least two antidepressant trials of adequate doses and duration (i.e., have failed $\geq$ 2 adequate antidepressant trials).

2.2.2 Interventions

Intranasal esketamine in any dosage for the primary treatment of depression, administered with antidepressant.

2.2.3 Comparators

Placebo (a solution with a bittering agent added to simulate the taste of the esketamine solution) or active placebo, administered with antidepressant.

2.2.4 Study Outcomes

The primary outcome is the total number of TEAEs during the acute treatment phase (described as treatment phase / induction phase / blinded phase in trials), irrespective of event type. TEAEs relevant to the use of esketamine include dissociation, sedation, nausea, dizziness, vertigo, headache, abnormal heart rate (atrial fibrillation, extrasystoles, increased heart rate, palpitations, sinus tachycardia, tachycardia), hypertension (increased diastolic blood pressure, increased systolic blood pressure, increased blood pressure, hypertension, hypertensive crisis, hypertensive heart disease) and cardiovascular events (angina pectoris, cardiac failure acute, chest discomfort, chest pain (Ochs-Ross et al. 2022; Doherty et al. 2020; Nikayin and Sanacora 2022)).

The primary objective is to evaluate whether sex (binary: male/female), age (continuous), pre-existing hypertension condition (binary: normotensive, hypertensive) and associated anti-depressants (binary: SSRI vs. SNRI) moderate the association between treatment and adverse events.

2.2.5 Study Design

Double-blind, randomised, placebo-controlled trials. Trials that excluded participants with pre-existing hypertensive conditions will be excluded.

3 Statistical Analysis

3.1 General Context

The goal is to perform a secondary analysis of trials assessing the efficacy of esketamine, that is, to address a new research question using this existing dataset. Access to the clinical trial data is granted via the Yale University Open Data Access (YODA) project.

3.2 Software

All analyses will be performed using R version 4.3.0 or higher.
For the analysis, we will use R packages such as `tidyverse`, `dplyr`, `meta`, `metafor`, `lme4`, `logistf`, `stringr`, `ordinal`, `lmerTest` and `ggplot2`.

3.3 Meta-analysis

Objective:
The primary objective is to evaluate whether sex, age, blood pressure or associated anti-depressants moderate the association between treatment and adverse events. The primary outcome will be analysed separately for each moderator using one-stage IPDMA.

Sex will be evaluated as a binary moderator (Male vs. Female). Baseline cardiovascular status will be evaluated as a binary moderator, classifying participants as hypertensive (Baseline systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or documented history) versus normotensive. Concomitant anti-depressants will be evaluated as a binary class moderator (SSRI vs. SNRI), restricting the concomitant medication safety analysis to participants actively receiving these two primary background therapeutic classes at baseline to evaluate the differential impact of noradrenergic versus serotonergic reuptake inhibition on acute post-dose safety signals. Age will be modeled as a continuous moderator to retain maximum statistical power and use data from both adult (18–64) and geriatric (≥ 65) trials.
Analysis Plan:
Separate one-stage mixed-effects negative binomial regression models will be fitted for each prespecified moderator. The outcome will be analysed using a one-stage mixed-effects negative binomial regression model. Treatment group, subgroup, i.e. the moderator, and the treatment subgroup interaction term will be included as fixed effects. The trial identifier will be included as a random intercept to account for clustering of participants within studies.
The continuous moderator age will be mean-centred across the pooled dataset prior to modelling. The interaction term (Treatment $\times$ Age) will assess whether the association

between treatment and the number of TEAEs varies with age. Age will be included as a continuous fixed effect together with the treatment group and the (Treatment × Age) interaction term in the mixed-effects negative binomial model.

Incidence rate ratios, the corresponding 95% confidence intervals and p-values for the interaction terms will be reported for all moderators.

We will include dosage as a covariate. This covariate differentiates between different fixed dosages of esketamine, e.g. 56mg or 84mg and flexible dosage.

Primary to the analysis, the linearity assumption for continuous age moderator will be verified graphically.

As the primary outcome is a composite outcome, we will also conduct separate analyses by adverse event type, including cardiovascular, neuropsychiatric, and other categories of adverse events.

3.4 Quality Control

Data extraction will follow a standardized process, including mapping trial-specific variables to harmonized analysis variables, cross-checking against protocols. Quality control procedures include range and consistency checks, verification of randomization assignments, assessment of completeness for key variables. All data cleaning steps will be scripted and documented.

3.5 Reproducibility

This statistical analysis plan will be uploaded to OSF. All code will be shared in accordance with the FAIR principles (Findable, Accessible, Interoperable, Reusable) and clear guidance will be made available for researchers seeking access to the data.

4 Changes from Protocol

4.1 Protocol Deviations

All deviations from the original trial protocols relevant to this IPDMA will be documented.

4.2 Statistical analysis plan Amendments

Any amendments to this statistical analysis plan will be dated, versioned, and justified prior to analysis.

Doherty, Teodora, Ewa Wajs, Rama Melkote, Janice Miller, Jaskaran B Singh, and Michael A Weber. 2020. “Cardiac Safety of Esketamine Nasal Spray in Treatment-Resistant Depression: Results from the Clinical Development Program.” *CNS Drugs* 34 (3): 299–310.

Jones, Robyn R, Marlene P Freeman, Susan G Kornstein, et al. 2022. “Efficacy and Safety of Esketamine Nasal Spray by Sex in Patients with Treatment-Resistant Depression: Findings from Short-Term Randomized, Controlled Trials.” *Archives of Women’s Mental Health* 25 (2): 313–26.

Nikayin, Sina, and Gerard Sanacora. 2022. “Ketamine/Esketamine for Treatment-Resistant Depression.” In *Managing Treatment-Resistant Depression*. Elsevier.

Ochs-Ross, Rachel, Ewa Wajs, Ella J Daly, et al. 2022. “Comparison of Long-Term Efficacy and Safety of Esketamine Nasal Spray Plus Oral Antidepressant in Younger Versus Older Patients with Treatment-Resistant Depression: Post-Hoc Analysis of SUSTAIN-2, a Long-Term Open-Label Phase 3 Safety and Efficacy Study.” *The American Journal of Geriatric Psychiatry* 30 (5): 541–56.