

## **STATISTICAL ANALYSIS PLAN (MULTI-ANALYST RE-ANALYSIS)**

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### **Effect of Esketamine on Suicidal Thoughts in Adults with Major Depressive Disorder: Individual Participant Data Meta analysis**

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Team 2

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## List of Abbreviations and Definitions

TERM	Abbreviation / Definition
IPD	Individual Participant Data
MDD	Major Depressive Disorder
MADRS	Montgomery-Asberg Depression Rating Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
PO	proportional odd
PIMs	Probabilistic index models
MICE	multiple imputation with chain equations
MAP	meta-analytic predictive

# 1 Study Overview

This is a statistical analysis plan (SAP) for a individual participant data (IPD) meta-analysis (IPD-MA) using several clinical trials that studied the efficacy of esketamine on suicidality. The analysis is performed within the Yale Open Data Access (YODA) Project Platform [1]. YODA is an independent academic organization that provides access to individual participant data from clinical trials.

## 1.1 Study Aims

The main objective of this meta-analysis is to evaluate the efficacy of esketamine versus placebo on suicidal thoughts in adults with Major Depressive Disorder (MDD), measured by item 10 of Montgomery-Åsberg Depression Rating Scale (MADRS), in two pre-specified patient populations: (1) patients with treatment-resistant depression, and (2) patients with acute suicidality. In population 1 we study item 10 at Day 28/end of double-blind treatment. In population 2 we study item 10 at 24 hours post-dose.

The secondary objectives are:

1. To evaluate the efficacy of esketamine versus placebo on MADRS item 10 at the alternate endpoint timepoint, defined as 24 hours post-dose in treatment-resistant depression trials and Day 28/end of the double-blind treatment period in acute suicidality trials.
2. To evaluate the efficacy of esketamine versus placebo on the Columbia-Suicide Severity Rating Scale (C-SSRS) ideation severity subscale at Day 28/end of double-blind treatment (only available for treatment resistant depression trials)
3. To explore the incidence of suicide attempts recorded as adverse events across treatment arms during the double-blind period.

Separating populations of patients with treatment-resistant depression from patients with acute suicidality is clinically motivated, as these populations differ in baseline risk, illness chronicity, and expected timing of treatment response. This IPD meta-analysis leverages harmonized participant-level data to provide more precise and generalizable estimates of treatment effects than conventional aggregate-data meta-analyses.

# 2 Study Methods

## 2.1 Design

This study is an Individual Participant Data (IPD) meta-analysis and we use the PICO framework to synthesize evidence from multiple randomized controlled trials identified in the YODA Project repository.

## 2.2 Participants, Interventions, Comparators, Outcomes (PICO)

- **Population:** adults (age  $\geq 18$ ), diagnosed with MDD, having treatment resistant depression (population 1) or suffering from acute suicidality (population 2).
- **Intervention:** Esketamine that was administered as an augmentation to a standard of care or as monotherapy
- **Comparator:** Placebo was administered as an augmentation to a standard of care or as monotherapy.
- **Outcome**
  - Primary outcome: Suicidal thoughts score according to the item 10 score from the MADRS.
  - Secondary outcomes are suicide ideation score according to C-SSRS.

## 2.3 Timepoints and Study Outcomes

### 2.3.1 Timepoints Definition

Timepoints are defined a priori at baseline, 24 hours post-dose, and Day 28 (end of treatment). Baseline is defined as the last assessment prior to the first dose of study treatment. For trials with patients showing acute suicidality, the primary endpoint is 24 hours post-dose, defined as the assessment recorded at 24 hours after the first dose, or,

if an exact 24 hour assessment is not available, the assessment closest to 24 hours after the first dose. For trial on patients with treatment resistant depression, the primary endpoint is Day 28, defined as the assessment closest to Day 28 within a Day 25–28 window; if multiple assessments fall within this window, the latest assessment within the window will be used. If an assessment is not available within the relevant window, the endpoint will be treated as missing for that participant at that timepoint.

### 2.3.2 Primary Outcome

- **Outcome Measure Title:** MADRS item 10 (suicidal thoughts)
- **Outcome Measure Description:** MADRS item 10 (suicidal thoughts) assesses the presence, frequency, and severity of suicidal ideas. The rater chooses the single best-fitting severity level: 0 = no suicidal thoughts; 1 = occasional thoughts that life is not worth living; 2 = recurrent thoughts of death or self-harm without plans or intent; 3 = more frequent or serious suicidal ideas; 4 = persistent suicidal ideation with more concrete thoughts about suicide; 5 = strong suicidal ideation with emerging intent and/or planning elements; 6 = explicit suicidal intent and/or clear planning or preparations, potentially including suicidal behaviour [2]. Clinically, a 1-point increase on MADRS item 10 reflects a meaningful stepwise worsening in the frequency or intensity of suicidal thoughts, while scores of 0–1 generally indicate minimal or absent suicidal ideation.
- **Outcome Measure Timeframe:** We will conduct two primary analyses separately for two different patient populations (reflected by two different sets of trials):
  - For patients with treatment-resistant depression (Primary Analysis 1) we measure the number of levels changed between baseline to Day 28/end
  - For patients with acute suicidality (Primary Analysis 2) we quantify the number of levels changed between baseline to 24 hours post-dose.

### 2.3.3 Secondary Outcomes

#### Secondary Outcome 1

- **Outcome Measure Title:** MADRS item 10 (Suicidal thoughts)
- **Outcome Measure Description:** as defined under the Primary Outcome.
- **Outcome Measure Timeframe:** The alternate endpoint timepoint relative to the primary endpoint for each trial subset:
  - Trials on patients with treatment-resistant depression: Baseline to 24 hours post-dose
  - Trials with patients suffering under acute suicidality: Baseline to Day 28/end of double-blind treatment

This analysis allows assessment of the short-term (24-hour) effect of esketamine in patients with treatment-resistant depression and the more sustained (Day 28) effect in patients with acute suicidality, providing a complementary view of the temporal profile of treatment effects on suicidal thoughts.

#### Secondary Outcome 2

- **Outcome Measure Title:** C-SSRS Ideation Severity Subscale
- **Outcome Measure Description:** C-SSRS Ideation Severity Subscale is an ordinal measure derived from five ideation categories assessed at each evaluation, with the severity score defined as the most severe category endorsed. The categories are: 1 = wish to be dead; 2 = non-specific active suicidal thoughts; 3 = active suicidal ideation with method; 4 = active suicidal ideation with intent (without a specific plan); 5 = active suicidal ideation with specific plan and intent. Depending on the trial/version, a category of 0 (no ideation) may also be recorded when none of the ideation categories are endorsed. The assessment time frame (e.g., past month at baseline and/or since last visit at other visits) will follow the trial-specific C-SSRS administration [3].
- **Outcome Measure Timeframe:** Baseline to Day 28/end of double-blind treatment (Only available in treatment-resistant depression trials according to the trial protocols)

### 2.3.4 Study Eligibility Criteria

Eligible trials must meet all of the following inclusion criteria:

1. Randomized, double-blind, placebo-controlled clinical trial;
2. Investigating the effect of esketamine;
3. Adult patients (age  $\geq 18$ );
4. Patients diagnosed with MDD

## 3 Statistical Analysis

### 3.1 Analysis of the Primary Endpoints

We assess the overall average treatment effect across trials with a one-stage IPD MA using baseline adjusted proportional odds mixed model with trial-level random intercepts [4]. Let  $Y_{ij} \in \{1, \dots, K\}$  denote the ordinal endpoint for subject  $i$  in trial  $j$  at the analysis time point (e.g., Day 28 or 24h), with larger values indicating more severe outcome. Let  $A_{ij} \in \{0, 1\}$  indicate treatment assignment (1=treatment, 0=control). The baseline ordinal score will be included as a categorical covariate unless otherwise stated. For cutpoints  $k = 1, \dots, K-1$ , we model the cumulative probabilities as

$$\text{logit}\{\Pr(Y_{ij} \leq k \mid A_{ij}, X_{ij}, b_j)\} = \alpha_k - \beta_{\text{trt}} A_{ij} - \gamma^\top X_{ij} - b_j, \quad (1)$$

where  $\alpha_k$  are cutpoint-specific intercepts,  $X_{ij}$  denotes the baseline covariate vector (including baseline score indicators), and  $b_j$  is a trial-specific random intercept with

$$b_j \sim N(0, \tau^2). \quad (2)$$

The parameter  $\beta_{\text{trt}}$  is the common (across cutpoints and across trials) log-odds ratio comparing treatment vs. control, conditional on  $X_{ij}$  and  $b_j$ . The null hypothesis is:

$$H_0 : \beta_{\text{trt}} = 0 \quad \text{vs.} \quad H_1 : \beta_{\text{trt}} \neq 0,$$

We will assess the proportional odds (PO) assumption for the treatment effect by comparing the PO model to a partial proportional odds model that allows cutpoint-specific treatment effects for treatment (i.e.,  $\beta_{\text{trt},k}$  varies with  $k$ ), using a likelihood ratio test where feasible.

$$\text{logit}\{\Pr(Y_{ij} \leq k \mid A_{ij}, X_{ij}, b_j)\} = \alpha_k - \beta_{\text{trt},k} A_{ij} - \gamma^\top X_{ij} - b_j, \quad k = 1, \dots, K-1. \quad (3)$$

If PO is not supported, the primary analysis will proceed with the partial proportional odds mixed model and inference will be based on a joint test of  $H_0 : \beta_{\text{trt},1} = \dots = \beta_{\text{trt},K-1} = 0$ .

In addition to odds ratios, marginal (standardized) treatment contrasts (e.g., differences in predicted category probabilities and/or a favourable-outcome risk difference) will be computed by integrating over the trial random intercept distribution and averaging over the observed baseline distribution.

If the primary model fails to converge or yields numerically unstable estimates after simplifying the trial component (e.g., trial as a fixed effect), we will fit an equivalent Bayesian proportional-odds mixed model with weakly informative priors to obtain stable estimates for the primary estimand.

An example code for the primary analysis:

```
library(ordinal)

# Suppose:
# y = ordinal outcome
# trt = 0/1 (0=control, 1=treated)
# x1, x2, x3 = baseline covariates
# trial_id is a factor for different trials
df$y <- ordered(df$y)
```

```
# P0 mixed model
fit_po <- clmm2(y ~ trt + x1 + x2 + x3, random = trial_id, data = df, link = "logit")
summary(fit_po)

# partial P0 mixed model
fit_npo <- clmm2(y ~ trt + x1 + x2 + x3, random = trial_id, data = df, link = "logit")
summary(fit_npo)

# likelihood ratio test
print(anova(fit_po, fit_npo))

# Bayesian alternative, if needed
library(brms)

bayes_PO <- brm(formula = y ~ trt + x1 + x2 + x3 + (1 | trial_id), data = df,
family = cumulative(link = "logit"))
summary(bayes_PO)
```

## 3.2 Sensitivity Analyses on the Primary Endpoints

For sensitivity analyses of the primary endpoint, we will apply baseline adjusted proportional odds (or partial proportional odds) fixed effect model.

Additionally, we assess the impact of each trial included in the primary analysis with a leave-one-out method, and visualize the variability of the estimated treatment effect.

### 3.2.1 Non-parametric approaches

Here we code for each patient the change of the outcome score with respect to baseline, negative values are coded if the outcome deteriorates, positive numbers give the levels of improvement. For the MADRS (item 10) low scores are better compared to higher score. The minimum is 0 and the maximum is 6. Theoretically there are 13 values between -6 to 6. In a first step, a ROC curve for each trial is calculated, comparing the level changes between both treatment groups. For each trial, the ROC curve will be plotted. Finally, the AUC of each trial-specific ROC is determined and its 95% confidence interval. Here we follow [5]. Based on this we perform a two level IPD meta-analysis by providing a meta-analysis over the trial specific AUC curves. The results are presented in a forest plot. Here the AUC is quantifying the probability that under treatment changes are in direction improvement: The probability that a patient randomly chosen from the placebo group has less improvement compared to a randomly chosen patient from the treatment group.

In order to look at a stratified analysis within trials, we use stratified versions of all three—win ratio, win odds, and win difference (net benefit). Within the trial we perform Mantel–Haenszel–type pooling (stratified win statistics) or inverse-variance pooling (fixed-effect meta-analytic style). The pooled win statistics are summarized by a random effects meta-analysis. Results are presented by forest plots.

### 3.2.2 Probabilistic Index Model analysis

Let  $Y$  be an ordinal outcome with  $K$  ordered categories (larger values indicate better outcomes),  $A \in \{0, 1\}$  a treatment indicator (0 = Placebo, 1 = Esketamine), and  $Z$  a vector of baseline covariates.

**Probabilistic index:** For two independently sampled subjects  $i$  and  $j$  with covariate vectors  $X_i = (A_i, Z_i)$  and  $X_j = (A_j, Z_j)$ , define the probabilistic index.

$$PI(X_i, X_j) := \Pr(Y_i \leq Y_j \mid X_i, X_j) = \Pr(Y_i < Y_j \mid X_i, X_j) + \frac{1}{2} \Pr(Y_i = Y_j \mid X_i, X_j). \quad (4)$$

The term  $\frac{1}{2} \Pr(Y_i = Y_j)$  assigns half weight to ties.

**PIM regression model:** A PIM specifies  $PI(X_i, X_j)$  through a link function  $g(\cdot)$  as

$$g(PI(X_i, X_j)) = \eta(X_i, X_j) = (X_j - X_i)^\top \beta, \quad (5)$$

where  $X_j - X_i$  denotes the componentwise difference and  $\beta$  is a parameter vector. Using the logit link  $g(u) = \log\{u/(1-u)\}$  yields

$$\text{logit}(PI(X_i, X_j)) = \beta_A(A_j - A_i) + \beta_Z^\top(Z_j - Z_i). \quad (6)$$

**Adjusted treatment effect:** The covariate-adjusted treatment effect is defined as the probability that a treated subject has a better outcome than a control subject *at the same covariate level*:

$$PI_{\text{adj}}(Z) := \Pr(Y_{A=0} \preceq Y_{A=1} \mid Z) = \Pr(Y_{A=0} < Y_{A=1} \mid Z) + \frac{1}{2} \Pr(Y_{A=0} = Y_{A=1} \mid Z). \quad (7)$$

Under (6) without treatment-covariate interaction terms,  $PI_{\text{adj}}(Z)$  does not depend on  $Z$  and equals

$$PI_{\text{adj}} = \text{expit}(\beta_A) = \frac{\exp(\beta_A)}{1 + \exp(\beta_A)}. \quad (8)$$

Values  $PI_{\text{adj}} > 0.5$  indicate a beneficial treatment effect (stochastically larger outcomes under treatment), while  $PI_{\text{adj}} = 0.5$  corresponds to no difference.

**Related effect measures:** Two equivalent summaries are

$$WO = \frac{PI_{\text{adj}}}{1 - PI_{\text{adj}}} = \exp(\beta_A), \quad (\text{win odds}) \quad (9)$$

$$WD = 2 PI_{\text{adj}} - 1, \quad (\text{win difference / net benefit}). \quad (10)$$

They reflect measures we proposed in the section above.

**Inference:** Let  $\hat{\beta}_A$  denote the estimated treatment coefficient and  $\widehat{SE}(\hat{\beta}_A)$  its standard error. A Wald-type 95% confidence interval for  $\beta_A$  is

$$\hat{\beta}_A \pm 1.96 \widehat{SE}(\hat{\beta}_A), \quad (11)$$

which can be transformed to a confidence interval for  $PI_{\text{adj}}$  via the expit map:

$$\left[ \text{expit}\left(\hat{\beta}_A - 1.96 \widehat{SE}(\hat{\beta}_A)\right), \text{expit}\left(\hat{\beta}_A + 1.96 \widehat{SE}(\hat{\beta}_A)\right) \right]. \quad (12)$$

A short example of the trial specific analysis looks as follows:

```
library(pim)

# Suppose:
# y = ordinal outcome
# trt = 0/1 (0=control, 1=treated)
# x1, x2, x3 = baseline covariates

df$y <- ordered(df$y) # or keep numeric

fit <- pim(y ~ trt + x1 + x2 + x3, data = df, link = "logit")
summary(fit)

beta_trt <- coef(fit)["trt"]
se_trt <- sqrt(diag(vcov(fit))["trt"])

PI_adj <- plogis(beta_trt)
CI_beta <- beta_trt + c(-1, 1) * qnorm(0.975) * se_trt
CI_PI <- plogis(CI_beta)

PI_adj
CI_PI
```



**Meta-analysis:** PIMs per study will be presented in a forest plot and a random effect meta-analysis of the trial specific results will be calculated.

### 3.2.3 Handling of missing values

Impact of missing values in primary endpoints will be assessed by comparing results from imputed dataset. We will impute the ordinal outcomes using multiple imputation with chain equations (MICE) and summarize the findings following Rubin's rule.

## 3.3 Subgroup Analyses

Pre-specified subgroup analyses will be limited and conducted by including treatment by subgroup interaction terms in the primary model. Subgroups will be defined using baseline demographic and clinical characteristics, including (1) age, (2) gender, (3) baseline depression severity, and (4) comorbid personality disorder. These subgroup analyses will be performed only where the relevant variables are available and comparably defined across trials; otherwise, they will be reported as not feasible for the affected trial subset.

## 3.4 Analysis of the Secondary Endpoints

Secondary outcome 1 is the same measure as the primary endpoint, but on alternate timepoint as defined in section 2.3.3 so will be analyzed similarly. Secondary outcomes 2 C-SSRS Ideation Severity Subscale will be assessed as ordinal outcome using the same analysis framework as in section 3.1, if data is available. If the secondary analyses is conducted on a subset of the trials in section 3.1, we will reassess the primary outcome on the same subset for comparison.

The secondary endpoint of suicide attempt will be analyzed as a binary outcome over the prespecified follow-up period (up to Day 25/28). Treatment effects will be estimated within trials using logistic regression and pooled across trials using a random-effects meta-analysis. In the presence of rare events or separation, penalized likelihood methods (e.g., Firth correction) may be applied at the trial level.

## 3.5 Exploratory Analyses

### 3.5.1 Longitudinal modeling

As an exploratory analysis to assess short-term and long-term treatment effects, the primary outcome will be analyzed longitudinally using a proportional-odds mixed model. Time will be defined as hours since baseline and modeled flexibly using splines to accommodate potentially non-linear short- and long-term trends [6]. Individual-level trajectory plots (spaghetti plots) and arm-specific mean profiles will be used descriptively to visualize short-term ( $\leq 24$  hours) and longer-term (up to Day 28) trajectories and to assess the adequacy of the time specification (e.g., spline complexity and knot placement). If warranted by convergence issues or lack of model stability, the time structure will be simplified (e.g., fewer knots or a piecewise linear function with a knot at 24 hours). Short- and long-term treatment effects will be assessed via a treatment  $\times$  time interaction. The model will adjust for baseline outcome and include random intercepts for trial and patient. Treatment effects will be summarized as model-based marginal contrasts at prespecified post-baseline time points. This longitudinal analysis is intended to explore patterns of change in suicidal thoughts over time, rather than to redefine the primary endpoint. Accordingly, inferences from the longitudinal model will be considered supportive and hypothesis-generating.

### 3.5.2 Modeling primary outcome as continuous outcome

As an exploratory sensitivity analysis, the primary outcome will additionally be analyzed as a continuous endpoint using change from baseline, reflecting a commonly used analytical approach in the field. A one-stage IPD meta-analysis will be conducted using a linear mixed-effects model with fixed treatment effect and random intercept for trial, adjusting for baseline outcome. The mean treatment difference at Day 28 will be estimated and compared qualitatively with results from the primary ordinal analysis to assess consistency of conclusions across outcome scales.

### 3.5.3 Selection of trials to derive informative priors (secondary use of data)

As an exploratory extension, we will investigate how the selection and availability of trials included in the IPD meta-analysis impact the construction of informative priors for treatment effects in a future trial for extrapolation. Using trial-specific treatment effect estimates from the meta-analysis, we will derive a meta-analytic predictive (MAP) prior and examine how its location and dispersion vary under alternative trial inclusion scenarios (e.g., all eligible trials vs restricted subsets reflecting data-sharing constraints or access through data-sharing platforms). Where feasible, we will quantify the resulting information content (e.g., via prior effective sample size on the treatment-effect scale [7]) to assess the sensitivity of prior informativeness to trial selection and data availability, thereby illustrating implications for the secondary use of shared clinical trial data.

## 4 Presentation of Results

For all primary and secondary analyses, treatment effects will be estimated primarily using one-stage IPD meta analysis models, where all eligible trials are analyzed jointly within a single modeling framework. For descriptive and visualization purposes, trial-specific treatment effect estimates will additionally obtained from separate trial-level analyses using the same outcome definitions and modeling assumptions. These trial-level estimates and their corresponding standard errors will be displayed in forest plots to illustrate the direction, magnitude and consistency of treatment effects across trials.

If applicable, two-stage pooled estimates may be included in forest plots for reference only. Given the limited number of trials in some of the analyses, these two-stage summaries will be interpreted cautiously. All statistical conclusions will be based on the one-stage analyses, trial-level and two-stage results are presented mainly to aid interpretation and graphical presentation.

## 5 References

### References

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