Statistical Analysis Plan (SAP)

Version 1

Full study title	Efficacy and safety of esketamine for "treatment resistant depression": registered report for a Systematic Review with an Individual Participant Data Meta-analysis of Randomized, Double-Blind, Placebo-Controlled Trials
Acronym	ESK-T-DEP
Prospero registry number	CRD42021290721
OSF registration	https://osf.io/xetvn
Study protocol version	V1.0
SAP version	V1

SAP revision history

Date	Document	Version	Description of and reason for change
08.2022	ESK-T-DEP_SAP	V1	Creation of the document

Roles and responsibility

Author	Name, date, and signature: Claude PELLEN 20/10/2022 
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1 Objectives

The main objective is to independently (independently from the sponsor) reappraise the efficacy of esketamine in "treatment resistant depression" (TRD) using an individual participant data meta-analysis methodology.

The secondary objectives are:

- to independently reappraise the safety of esketamine in the treatment of TRD
- and to explore moderating factors of esketamine efficacy and safety, including level of treatment resistance, participant age, site-specific effects, among others.

2 Study methods

2.1 Design

Systematic review and meta-analysis of individual participant data (IPD) derived from double-blind, randomised, placebo-controlled [placebo or active placebo] trials for the indication of TRD.

2.2 Participants, interventions, comparators, outcomes, and study design (PICOS)

Participants
Participants with TRD.
TRD refers to a depressive episode with inadequate response to at least two antidepressant trials of adequate doses and duration (i.e., have failed ≥ 2 adequate antidepressant trials). This definition includes "higher" level of "resistance" according to Thase and Rush staging method of treatment resistant depression.

There will be no age limit.

Interventions
Intranasal esketamine (with the following approved doses: 56 mg or 84 mg or "flexible" doses) for the primary treatment of depression.

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

Study design
Randomised controlled trials (initiation and continuation (i.e. maintenance) trials).

3 Trial population

3.1 Search strategy

Systematic searches will be conducted using PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL: https://www.cochranelibrary.com/central/about-central), Embase, ClinicalTrials.gov, Clinicaltrialsregister.eu, FDA, EMA and the manufacturer website. All records will be managed (and deduplicated) using Endnote.

3.2 Data collection and assessment of risk of bias

Selection and coding of the different study characteristics will independently be performed by two reviewers . A third reviewer will arbitrate in case of disagreement. A data extraction sheet based on the Cochrane Handbook for Systematic Reviews of Interventions guidelines will be developed.

Studies appearing to duplicate authors, treatment comparisons, sample sizes and outcomes will be checked against one other to avoid any duplicates and to avoid integrating data from several reports on the same study.
For each included study, information will be extracted regarding: a) characteristics of the study [year, country, selection criteria, co-treatments (psychological interventions and their type), number of arms, funding]; b) type of intervention (treatments and comparators, duration). Importantly, mean characteristics of the trial participants and outcome measures will not be extracted, as we will rely on IPD.

Two researchers will independently assess each trial for risk of bias according to the Cochrane Collaboration tool for assessing risk of bias in its current version, RoB2 [21].

A data sharing request (IPD, analytical code, metadata, study reports, statistical analysis plan and any other relevant documents) will be sent to the relevant data sharing platforms and/or sponsor and /or authors. Importantly, data and metadata of the pivotal trials are available on the YODA project (https://yoda.yale.edu/jj-available-data).

3.3 Flowchart

In terms of strategy the systematic review search criteria will include all studies of esketamine for the primary treatment of depression. The IPD analysis will then be restricted to participants with TRD within the included studies (i.e., have failed > 2 adequate antidepressant trials).

The PRISMA-IPD flowchart template will be used.

4 Analysis

4.1 Generality

4.1.1 Software

All the analyses will be performed with R (R core Team, 2021).

4.1.2 Identification of variables of interest

See the appendix table “List of variables of interest”.

4.2 Reanalysis of sponsor’s primary outcome

Reanalysis of the primary outcomes(s) of the study following the initial protocol and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use by a statistician who will have no access to study reports, journal publications, statistical analysis plan, or analytical code.
Reanalyses will be based on the latest version of the protocol issued before database lock and unblinding. If this information is not available, the date of the last visit of the last participant will be used as a proxy. In case of missing information for these dates, the study authors will be contacted.
Below are the tables ad figures to be completed during the reanalysis.

Date of database lock	
Date of database unblinding	
Date of the last visit of the last participant	
Date and version of the latest version of the protocol issued before database lock and unblinding	

Table 1: Dates of database lock, unblinding, last visit of the last participant and latest version of the protocol

	Information in the study documents	**If not present, replace according to ICH section**	**Information used in the reanalysis**
Objectives and hypotheses		ICH E6	
Analysis method		ICH E9, point 5	
Handling missing data		ICH E9, point 5.3	
Protocol violations		ICH E9, point 2.3 ICH E6, point 6	
Analysis sets		ICH E9, point 5.2	

Table 2: Statistical analysis plan of study

Description of any deviations from the protocol
Any change, especially outcome switching, identified between the first version of the protocol and the version used for the reanalysis of the primary outcome will be tracked and described.

Studies	Consent	Selection	Follow-up	Treatment	Others	At least one deviation
Study 1	N	N	N	N	N	N

Table 3: Description of the deviations per study

Table 4: List of deviations per study with no subject ID

Results of the reanalysis

P-value	
Effect size	
Changes from the initial protocol	

Table 5: Results of the reanalysis

Exploration of center effect

Center effect is explored by performing sensitivity analyses removing a center at a time.

	Without centre 1	Without centre 2	Without centre 3	…		
P-value						
Effect size						

Table 6: Results of the sensitivity analyses

X-axis: effect size by increasing values
Y-axis: each sensitivity analysis

Figure 1

Data integrity issues mentioned in the FDA appraisal

Not performed by the statistician who reanalyses the studies.

Comparison of the analysis results with the analyses reported in the FDA reports, European public assessment reports, study reports & publications

Not performed by the statistician who reanalyses the studies.

Document	P-value	Effect size

Table 7: Results from all available documents (FDA reports, European public assessment reports, study reports & publications)

4.3 Meta-analyses

4.3.1 Initiation studies

4.3.1.1 Efficacy outcomes

4.3.1.1.1 Meta-analysis of primary outcome

MADRS after at least 4 weeks

Type of outcome	Continuous outcome.

Meta-analysis	Two-stage IPD meta-analysis of continuous outcome
	- First stage:
	  o Methods: in line with each reanalysis (cf. section 4.2). The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment.
	  o Results: mean final score, standard deviation, number of subjects, per group.
	- Second stage:
	  o Package *meta*, function *metacont*.
	  o Inverse variance method.
	  o Summary measure: mean difference.
	  o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic.
	  o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
	
	Mean differences in MADRS observed (point estimates and confidence intervals) will be compared with 0 (absence of difference) and 6.5 points (the threshold defined *a priori* in initiation studies) on a forest plot (visual comparison).

Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Certainty of evidence	Rated by GRADE; not performed by the statistician.

4.3.1.1.2 Meta-analysis of secondary outcomes

4.3.1.1.2.1 Outcome assessed at week 1

MADRS at week 1

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT

	principle) and not the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package *meta*, function *metacont*. o Inverse variance method. o Summary measure: mean difference. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach. Mean differences in MADRS observed (point estimates and confidence intervals) will be compared with 0 (absence of difference) and 6.5 points (the threshold defined *a priori* in initiation studies) on a forest plot (visual comparison).
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.1.1.2.2 Outcomes assessed at the end of treatment

Suicide/suicide attempt

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.

Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Suicidal ideations, e.g. Beck Scale for Suicidal Ideation (BSS)

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package meta, function metacont. o Inverse variance method. o Summary measure: mean difference. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Remission (MADRS score <8 if no binary)

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk.

	○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Sheehan Disability Scale

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

PHQ-9

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment.

	○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.1.1.2.3 Outcomes assessed at the last follow-up visit post-treatment

Description of treatments received

		Treatment received at the last follow-up visit		
		Esketamine	**Placebo**	**Total**
Treatment allocation at randomisation	**Esketamine**	N	N	N
	Placebo	N	N	N
	Total	N	N	N

Table 8: Description of treatment allocations and treatments received at the last follow-up visit

Suicide/suicide attempt

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: number of subjects with events, total number of subjects, per group. - Second stage: ○ Package meta, function metabin. ○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence

	interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Suicidal ideations, e.g. Beck Scale for Suicidal Ideation (BSS)

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package meta, function metacont. o Inverse variance method. o Summary measure: mean difference. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

MADRS

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package meta, function metacont. o Inverse variance method. o Summary measure: mean difference.

	○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach. Mean differences in MADRS observed (point estimates and confidence intervals) will be compared with 0 (absence of difference) and 6.5 points (the threshold defined *a priori* in initiation studies) on a forest plot (visual comparison).
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Remission (MADRS score <8 if no binary)

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: number of subjects with events, total number of subjects, per group. - Second stage: ○ Package meta, function metabin. ○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Sheehan Disability Scale

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage:

	○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

PHQ-9

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.1.2 Safety outcomes

4.3.1.2.1 Outcomes assessed at the end of treatment

Serious adverse events

Type of outcome	Count outcome, i.e. number of events per participant.
Meta-analysis	Two-stage IPD meta-analysis for count outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of events, person time at risk, per group. - Second stage: o Package meta, function metainc. o Inverse variance method. o Summary measure: incidence rate ratio. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dropout for any cause

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.

Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dropout due to adverse events

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Adverse events

Type of outcome	Count outcome, i.e. number of events per participant.
Meta-analysis	Two-stage IPD meta-analysis for count outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of events, person time at risk, per group. - Second stage: o Package meta, function metainc. o Inverse variance method. o Summary measure: incidence rate ratio. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence

	interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Blood pressure

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package meta, function metacont. o Inverse variance method. o Summary measure: mean difference. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dissociation

Type of outcome	Binary outcome.
Meta-analysis	In case of dissociation is not explicitly reported, the AEs will be assessed in a blind manner (i.e. without knowledge of the treatment group) and discussed by a clinician. Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin.

	○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Sedation

Type of outcome	Binary outcome.
Meta-analysis	In case of sedation is not explicitly reported, the AEs will be assessed in a blind manner (i.e. without knowledge of the treatment group) and discussed by a clinician. Two-stage IPD meta-analysis for binary outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. ○ Results: number of subjects with events, total number of subjects, per group. - Second stage: ○ Package meta, function metabin. ○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.1.2.2 Outcomes assessed at the last follow-up visit post-treatment

Serious adverse events

Type of outcome	Count outcome, i.e. number of events per participant.

Meta-analysis	Two-stage IPD meta-analysis for count outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of events, person time at risk, per group. - Second stage: o Package meta, function metainc. o Inverse variance method. o Summary measure: incidence rate ratio. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dropout for any cause

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dropout due to adverse events

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Adverse events

Type of outcome	Count outcome, i.e. number of events per participant.
Meta-analysis	Two-stage IPD meta-analysis for count outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of events, person time at risk, per group. - Second stage: o Package meta, function metainc. o Inverse variance method. o Summary measure: incidence rate ratio. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).

Level of evidence	Rated by GRADE; not performed by the statistician.

Blood pressure

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package meta, function metacont. o Inverse variance method. o Summary measure: mean difference. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dissociation

Type of outcome	Binary outcome.
Meta-analysis	In case of dissociation is not explicitly reported, the AEs will be assessed in a blind manner (i.e. without knowledge of the treatment group) and discussed by a clinician. Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence

	interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Sedation

Type of outcome	Binary outcome.
Meta-analysis	In case of sedation is not explicitly reported, the AEs will be assessed in a blind manner (i.e. without knowledge of the treatment group) and discussed by a clinician. Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.1.3 Moderators of esketamine efficacy

Based on the individual data, the interactions will be assessed first with a two-stage approach. One-stage IPD meta-analysis may be used if necessary. The use of two-stage approach is a change from the initial protocol that was made to handle the risk for ecological bias inherent with the one-stage approach.

Impact of resistance stage

Each participant will be classified according to Thase and Rush resistance stages in accordance with their baseline characteristics. In case of missing data, the possibility to classify participants will be explored in a blind manner (i.e. without knowledge of the treatment group) with a clinician.

Stage	**Definition**
Stage I	Failure of 1 adequate trial of 1 major class of antidepressants
Stage II	Failure of 2 adequate trial of 2 major class of antidepressants
Stage III	Stage II resistance + failure of an adequate trial of a tricyclic agent
Stage IV	Stage III resistance + failure of an adequate trial of a monoamine oxidase inhibitor
Stage V	Stage IV resistance + a course of bilateral electroconvulsive therapy

Table 9: Thase and Rush staging method of treatment resistant depression

Two-stage IPD meta-analysis	First stage: - Outcome: MADRS after at least 4 weeks (continuous outcome). - Covariate: resistance stage (quantitative outcome, 1, 2, 3, 4, 5). - Estimation of the interaction term, between resistance stage and treatment group, and its variance in each study, in line with each reanalysis. - The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. - Results: interaction term, standard deviation, number of subjects, per group. Second stage: - Outcome: interaction term (continuous outcome). - Package meta, function metacont. - Inverse variance method. - Summary measure: interaction effect. - Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. - In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
One-stage IPD meta-analysis	Outcome: MADRS after at least 4 weeks (continuous outcome). $MADRS_{ij} = \phi_i + \beta 1_i\, z_{ij} + \theta_i\, treat_{ij} + \gamma_W\, (treat_{ij} * (z_{ij} - \bar{z}_i)) + \varepsilon_{ij} \quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$ i = 1 to k trials j participants Esketamine group ($treat_{ij} = 1$), control group ($treat_{ij} = 0$) $MADRS_{ij}$: outcome ϕ_i : control effect (intercept term) θ_i : treatment effect ε_{ij} : residual error (error term) γ_W = within-study interaction term z_{ij} : participant-level covariate Model should allow: - One intercept for each study (stratification) - One treatment effect for each study (random effects)

	- The separation of within-study and across-study interaction (by centering covariates and including their mean or proportion) - One within-study interaction effect for each study (random effects) - One residual variance for each study (stratification) - Uncorrelated random effects
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot.
Level of evidence	Rated by GRADE; not performed by the statistician.

Impact of age

Two-stage IPD meta-analysis	First stage: - Outcome: MADRS after at least 4 weeks (continuous outcome). - Covariate: age (continuous outcome). - Estimation of the interaction term, between age and treatment group, and its variance in each study, in line with each reanalysis. - The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. - Results: interaction term, standard deviation, number of subjects, per group. Second stage: - Outcome: interaction term (continuous outcome). - Package meta, function metagen. - Inverse variance method. - Summary measure: interaction effect. - Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. - In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
One-stage IPD meta-analysis	Outcome: MADRS after at least 4 weeks (continuous outcome). $MADRS_{ij} = \phi_i + \beta 1_i\, z_{ij} + \theta_i\, treat_{ij} + \gamma_W\, (treat_{ij} * (z_{ij}-\bar{z}_i)) + \varepsilon_{ij}$ $\quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$ i = 1 to k trials j participants Esketamine group ($treat_{ij} = 1$), control group ($treat_{ij} = 0$) $MADRS_{ij}$: outcome ϕ_i : control effect (intercept term) θ_i : treatment effect ε_{ij} : residual error (error term) γ_W = within-study interaction term z_{ij} : participant-level covariate Model should allow: - One intercept for each study (stratification) - One treatment effect for each study (random effects) - The separation of within-study and across-study interaction (by centering covariates and including their mean or proportion) - One within-study interaction effect for each study (random effects)

	- One residual variance for each study (stratification) Uncorrelated random effects
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot.
Level of evidence	Rated by GRADE; not performed by the statistician.

Impact of per capita gross national income

Another sensitivity analysis will be performed to explore if efficacy varies according to the World Bank categorization into low, middle, and high income (https://data.worldbank.org/country) as initial evidence on antidepressants suggests that per capita gross national income is associated with trial results.

Study	High income country	Low, lower middle, and upper middle income country	Missing data
1	*Number of participants*	*Number of participants*	*Number of participants*
2	*Number of participants*	*Number of participants*	*Number of participants*
3	*Number of participants*	*Number of participants*	*Number of participants*
…	*Number of participants*	*Number of participants*	*Number of participants*

Table 10: Description of the per capita gross national income in each initiation study

Two-stage IPD meta-analysis	First stage: - Outcome: MADRS after at least 4 weeks (continuous outcome). - Covariate: per capita gross national income (binary outcome: high income countries vs. the other). - Estimation of the interaction term, between per capita gross national income and treatment group, and its variance in each study, in line with each reanalysis. - The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. - Results: interaction term, standard deviation, number of subjects, per group. Second stage: - Outcome: interaction term (continuous outcome). - Package meta, function metagen. - Inverse variance method. - Summary measure: interaction effect. - Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. - In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
One-stage IPD meta-analysis	Outcome: MADRS after at least 4 weeks (continuous outcome). $MADRS_{ij} = \phi_i + \beta 1_i\, z_{ij} + \theta_i\, treat_{ij} + \gamma_W\, (treat_{ij} * (z_{ij} - \bar{z}_i)) + \varepsilon_{ij}$ $\quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$ i = 1 to k trials j participants Esketamine group ($treat_{ij} = 1$), control group ($treat_{ij} = 0$) $MADRS_{ij}$: outcome ϕ_i : control effect (intercept term) θ_i : treatment effect ε_{ij} : residual error (error term) γ_W = within-study interaction term z_{ij} : participant-level covariate Model should allow:

	- One intercept for each study (stratification) - One treatment effect for each study (random effects) - The separation of within-study and across-study interaction (by centering covariates and including their mean or proportion) - One within-study interaction effect for each study (random effects) - One residual variance for each study (stratification) Uncorrelated random effects
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot.
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.2 Continuation studies

Only randomised continuation trials will be included in the meta-analysis.

4.3.2.1 Efficacy outcomes assessed at the end of the study

Relapse

Type of outcome	Censored outcome, principal outcome for continuation trials.

Meta-analysis	Two-stage IPD meta-analysis for time-to-event outcome
	- First stage:
	  o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment.
	  o Results: hazard ratio and its variance.
	- Second stage:
	  o Package meta, function metagen.
	  o Inverse variance method.
	  o Summary measure: hazard ratio.
	  o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic.
	  o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.

Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Suicide/suicide attempt

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage:

	○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: number of subjects with events, total number of subjects, per group. - Second stage: ○ Package meta, function metabin. ○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Suicidal ideations, e.g. Beck Scale for Suicidal Ideation (BSS)

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

MADRS

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: mean final score, standard deviation, number of subjects, per group. - Second stage: o Package meta, function metacont. o Inverse variance method. o Summary measure: mean difference. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach. Mean differences in MADRS observed (point estimates and confidence intervals) will be compared with 0 (absence of difference) and 6.5 points (the threshold defined *a priori* in initiation studies) on a forest plot (visual comparison).
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Remission (score <8 if no binary)

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic.

	○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Sheehan Disability Scale

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

PHQ-9

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont.

	○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.2.2 Safety outcomes assessed at the end of the study

Serious adverse events

Type of outcome	Count outcome, i.e. number of events per participant.
Meta-analysis	Two-stage IPD meta-analysis for count outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. ○ Results: number of events, person time at risk, per group. - Second stage: ○ Package meta, function metainc. ○ Inverse variance method. ○ Summary measure: incidence rate ratio. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dropout for any cause

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment.

	○ Results: number of subjects with events, total number of subjects, per group. - Second stage: ○ Package meta, function metabin. ○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dropout due to adverse events

Type of outcome	Binary outcome.
Meta-analysis	Two-stage IPD meta-analysis for binary outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. ○ Results: number of subjects with events, total number of subjects, per group. - Second stage: ○ Package meta, function metabin. ○ Inverse variance method. ○ Summary measure: relative risk. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Adverse events

Type of outcome	Count outcome, i.e. number of events per participant.
Meta-analysis	Two-stage IPD meta-analysis for count outcome - First stage:

	○ Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. ○ Results: number of events, person time at risk, per group. - Second stage: ○ Package meta, function metainc. ○ Inverse variance method. ○ Summary measure: incidence rate ratio. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Blood pressure

Type of outcome	Continuous outcome.
Meta-analysis	Two-stage IPD meta-analysis for continuous outcome - First stage: ○ Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. ○ Results: mean final score, standard deviation, number of subjects, per group. - Second stage: ○ Package meta, function metacont. ○ Inverse variance method. ○ Summary measure: mean difference. ○ Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. ○ In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Dissociation

Type of outcome	Binary outcome.

Meta-analysis	In case of dissociation is not explicitly reported, the AEs will be assessed in a blind manner (i.e. without knowledge of the treatment group) and discussed by a clinician. Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

Sedation

Type of outcome	Binary outcome.
Meta-analysis	In case of sedation is not explicitly reported, the AEs will be assessed in a blind manner (i.e. without knowledge of the treatment group) and discussed by a clinician. Two-stage IPD meta-analysis for binary outcome - First stage: o Methods: in line with each reanalysis. The participants will be analysed according to the treatment they receive at the time of outcome assessment. o Results: number of subjects with events, total number of subjects, per group. - Second stage: o Package meta, function metabin. o Inverse variance method. o Summary measure: relative risk. o Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. o In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence

	interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot. Funnel plot if applicable (> 10 studies).
Level of evidence	Rated by GRADE; not performed by the statistician.

4.3.2.3 Moderators of esketamine efficacy

Based on the individual data, the interactions will be assessed first with a two-stage approach. One-stage IPD meta-analysis may be used if necessary. The use of two-stage approach is a change from the initial protocol that was made to handle the risk for ecological bias inherent with the one-stage approach.

Impact of resistance stage

Each participant will be classified according to Thase and Rush resistance stages in accordance with their baseline characteristics. In case of missing data, the possibility to classify participants will be explored in a blind manner (i.e. without knowledge of the treatment group) with a clinician.

Two-stage IPD meta-analysis	First stage: - Outcome: MADRS at the end of the study (continuous outcome). - Covariate: resistance stage (quantitative outcome, 1, 2, 3, 4, 5). - Estimation of the interaction term, between resistance stage and treatment group, and its variance in each study, in line with each reanalysis. - The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. - Results: interaction term, standard deviation, number of subjects, per group. Second stage: - Outcome: interaction term (continuous outcome). - Package meta, function metagen. - Inverse variance method. - Summary measure: interaction effect. - Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. - In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
One-stage IPD meta-analysis	Outcome: MADRS at the end of the study (continuous outcome). $MADRS_{ij} = \phi_i + \beta 1_i\, z_{ij} + \theta_i\, treat_{ij} + \gamma_W\, (treat_{ij} * (z_{ij} - \bar{z}_i)) + \varepsilon_{ij}$ $\quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$ i = 1 to k trials j participants Esketamine group ($treat_{ij} = 1$), control group ($treat_{ij} = 0$) $MADRS_{ij}$: outcome ϕ_i : control effect (intercept term)

	θ_i : treatment effect ε_{ij} : residual error (error term) γ_W = within-study interaction term z_{ij} : participant-level covariate Model should allow: - One intercept for each study (stratification) - One treatment effect for each study (random effects) - The separation of within-study and across-study interaction (by centering covariates and including their mean or proportion) - One within-study interaction effect for each study (random effects) - One residual variance for each study (stratification) - Uncorrelated random effects
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot.
Level of evidence	Rated by GRADE; not performed by the statistician.

Impact of age

Two-stage IPD meta-analysis	First stage: - Outcome: MADRS at the end of the study (continuous outcome). - Covariate: age (continuous outcome). - Estimation of the interaction term, between age and treatment group, and its variance in each study, in line with each reanalysis. - The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. - Results: interaction term, standard deviation, number of subjects, per group. Second stage: - Outcome: interaction term (continuous outcome). - Package meta, function metagen. - Inverse variance method. - Summary measure: interaction effect. - Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic. - In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
One-stage IPD meta-analysis	Outcome: MADRS at the end of the study (continuous outcome). $MADRS_{ij} = \phi_i + \beta 1_i\, z_{ij} + \theta_i\, treat_{ij} + \gamma_W\, (treat_{ij} * (z_{ij}-\bar{z}_i)) + \varepsilon_{ij}$ $\quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$ i = 1 to k trials j participants Esketamine group ($treat_{ij} = 1$), control group ($treat_{ij} = 0$) $MADRS_{ij}$: outcome ϕ_i : control effect (intercept term) θ_i : treatment effect ε_{ij} : residual error (error term) γ_W = within-study interaction term

	z_{ij} : participant-level covariate Model should allow: - One intercept for each study (stratification) - One treatment effect for each study (random effects) - The separation of within-study and across-study interaction (by centering covariates and including their mean or proportion) - One within-study interaction effect for each study (random effects) - One residual variance for each study (stratification) Uncorrelated random effects
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot.
Level of evidence	Rated by GRADE; not performed by the statistician.

Impact of per capita gross national income

Another sensitivity analysis will be performed to explore if efficacy varies according to the World Bank categorization into low, middle, and high income (https://data.worldbank.org/country) as initial evidence on antidepressants suggests that per capita gross national income is associated with trial results.

Study	High income country	Low, lower middle, and upper middle income country	Missing data
1	*Number of participants*	*Number of participants*	*Number of participants*
2	*Number of participants*	*Number of participants*	*Number of participants*
3	*Number of participants*	*Number of participants*	*Number of participants*
…	*Number of participants*	*Number of participants*	*Number of participants*

Table 11: Description of the per capita gross national income in each continuation study

Two-stage IPD meta-analysis	First stage: - Outcome: MADRS at the end of the study (continuous outcome). - Covariate: per capita gross national income (binary outcome: high income countries vs. the other). - Estimation of the interaction term, between per capita gross national income and treatment group, and its variance in each study, in line with each reanalysis. - The participants will be analysed according to their allocated treatment at baseline (ITT principle) and not the treatment they receive at the time of outcome assessment. - Results: interaction term, standard deviation, number of subjects, per group. Second stage: - Outcome: interaction term (continuous outcome). - Package meta, function metagen. - Inverse variance method. - Summary measure: interaction effect. - Random effects will be used in case of heterogeneity defined as an I^2 index > 25% and/or significant heterogeneity ($p < 0.10$) detected using Cochran's Q test statistic.

	- In case of random effects, restricted maximum likelihood estimation (REML) estimation will be used and confidence interval will be derived by the Hartung-Knapp Sidik-Jonkman (HKSJ) approach.
One-stage IPD meta-analysis	Outcome: MADRS at the end of the study (continuous outcome). $MADRS_{ij} = \phi_i + \beta 1_i\, z_{ij} + \theta_i\, treat_{ij} + \gamma_W\, (treat_{ij} * (z_{ij} - \bar{z}_i)) + \varepsilon_{ij}$ $\quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$ i = 1 to k trials j participants Esketamine group ($treat_{ij} = 1$), control group ($treat_{ij} = 0$) $MADRS_{ij}$: outcome ϕ_i : control effect (intercept term) θ_i : treatment effect ε_{ij} : residual error (error term) γ_W = within-study interaction term z_{ij} : participant-level covariate Model should allow: - One intercept for each study (stratification) - One treatment effect for each study (random effects) - The separation of within-study and across-study interaction (by centering covariates and including their mean or proportion) - One within-study interaction effect for each study (random effects) - One residual variance for each study (stratification) Uncorrelated random effects
Sensitivity analysis	A sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis.
Plot	Forest plot.
Level of evidence	Rated by GRADE; not performed by the statistician.