KET01-IIT03: A Pilot, Open-label Phase II Trial of Adjunctive Treatment with Ketamine Hydrochloride Prolonged-Release Tablets (KET01) during the Initiation of Antidepressant Therapy in Major Depressive Disorder

Statistical Analysis Plan (SAP)

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1 Table of contents

2 Roles and responsibilities

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Role: Investigator

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Role: Study coordinator

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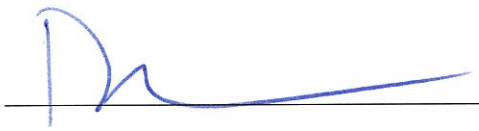
3 Signature

We have read this Statistical Analysis Plan carefully and believe that it contains all the necessary information to carry out the analyses in the KET01-IIT03 trial.



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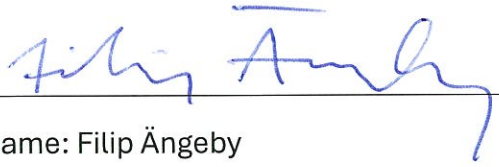

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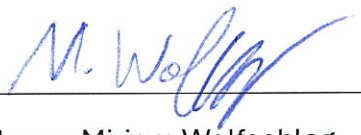

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4 List of abbreviations

AESI	Adverse event of Special Interest
CD-RISC-25	Connor-Davidsson Resilience Scale 25-items
CGI-E/S	Clinical Global Impression scale - Efficacy index/Severity of illness
C-SSRS	Columbia-Suicide Severity Rating Scale
FAS	Full analysis set
GAD-7	Generalized Anxiety Disorder 7-Item Scale
hs-CRP	high-sensitive C-reactive protein
IC	Informed consent
ICE	Intercurrent events
IL-6	Interleukin-6
InfDep score	Inflammatory depressive symptom score
ITT	Intention to treat
KET01	Ketamine Hydrochloride Prolonged-Release Tablets
LOCF	Last-observation-carried-forward
LPA	Low-Intensity Physical Activity
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MVPA	Moderate- to Vigorous Physical Activity
NA	Number of awakenings
NMDA	N-methyl-D-aspartate
PHQ-9	Patient Health Questionnaire 9-items
PPS	Per-protocol set
PT	Preferred term
SAF	Safety set
SAP	Statistical Analysis Plan
SE	Sleep efficiency
SED	Sedentary Behaviour
SOC	System organ class
TEAE	Treatment emergent adverse events
TNFα	Tumor necrosis factor alpha
TST	Total sleep time
WASO	Wake after sleep onset
WBC	White blood cell

5 Introduction

Conventional antidepressant treatments have a delayed onset, with full effect only after 4-6 weeks and a possible paradoxical increase of anxiety during the first weeks of treatment which is linked to an increase in suicide risk. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist which is widely used as an anesthetic and has shown anti-depressant effects, characterized by a fast onset and efficacy in difficult-to-treat patients. Administrations available today include intravenous infusions and a nasal spray, which give a fast peak of plasma ketamine and side effects such as dissociation.

In this study we will investigate the feasibility of the study protocol and safety of add-on KET01, an oral prolonged release ketamine hydrocloride tablet which gives a slower increase in plasma concentration and fever side effects.

The statistical analysis plan (SAP) was prepared in accordance with the protocol (v1.2) dated 2026-02-18.

6 Overview of study design and objectives

The overall objective of this study is to investigate KET01 as an add-on in depressed patients whom start a conventional treatment. As this is a small, open-label pilot study focused on feasibility, it is not powered to detect statistically significant effects; all analyses should therefore be considered exploratory.

Study objectives and endpoints:

The primary objective of this study is to evaluate the change in depressive symptom severity after one week of treatment with the KET01 as an adjunct to the initiation of a standard antidepressant. The primary outcome is the change in total Montgomery–Åsberg Depression Rating Scale (MADRS) score from baseline (day 1) to day 8 (last dosing day). Secondary objectives and endpoints are:

- *To evaluate the effect of KET01 on depression, anxiety and overall clinical global impression.*
- *To evaluate safety and tolerability of KET01.*
- *To evaluate if inflammatory markers change during treatment with KET01 and if this is associated with symptom improvement.*
- *To evaluate the relationship between KET01 epigenetic markers and resilience.*
- *To evaluate KET01-related changes in physical activity and sleep patterns.*
- *To investigate participant's lived experience of changes in mood during KET01 treatment.*

These objectives will be investigated using the following endpoints:

- Change in depressive symptoms at all post-baseline visits (MADRS)
- Change in disease severity (CGI-S), self-rated depressive symptoms (PHQ-9), self-rated inflammatory depressive symptoms (items # 3, 4 and 5 from PHQ-9) and self-rated anxiety symptoms (GAD-7)
- Change in clinical global impression (CGI-E)

7 Study design

This is an open label pilot study in which up to a total of 12 patients will receive add-on KET01 at four dosing days during the first eight days of antidepressant treatment. The trial will initiate with a screening period of a maximum of 30 days, during which patients will be assessed regarding eligibility criteria and current antidepressant treatment (if

any) will be washed out. At baseline, all patients will initiate treatment simultaneously with (1) a conventional antidepressant, once daily and (2) KET01 240 mg three times per week. In total, patients will receive four doses of the KET01. After the eight days KET01 treatment period, patients will be followed up two times during three weeks.

An overview of the study plan can be found below.

Figure 1

	Screening		Treatment					KET01 Follow-up	
Study Day	-30	-7 (-3)	1	2	3 (+1)	5 (±1)	8 (±1)	15 (±1)	29 (±2)
Week	-4	-1	0	0	0	0	1	2	4
Visit	1	2	3	4	5	6	7	8	9
Visit type	Site	Phone call	Site	Phone call	Site	Site	Site	Site	Site
Informed consent	•								
Demographics	•								
Medical history (incl ERDLEQ)	•								
Psychiatric history (DSM-5-TR)	•								
In-/Exclusion criteria	•		•						
Eligibility confirmation		•							
Start wash-out if needed		•							
Physical examination	•		•				•		•
12-lead ECG	•						•		•
Vital signs	•		•				•	•	•
Concomitant medications	•	•	•				•	•	•
Study drug dispensation			•[1]		•[1]	•[1]	•[1]		
Adverse events				•	•	•	•	•	•
MADRS	•		•		•	•	•	•	•
PHQ-9			•				•	•	•
GAD-7			•				•	•	•
CGI-S			•		•	•	•	•	•
CGI-E					•	•	•	•	•
CD-RISC-25			•				•		•
C-SSRS	•		•				•	•	•
Accelerometery	•	•	•	•	•	•	•	•	•
Qualitative interview									•
Blood collection	•		•				•	•	•
Urinalysis	•		•				•	•	•
Pregnancy test (urine)	•		•						•
Psychotropic drug panel (urine)	•		•				•	•	•

1: KET01 treatment is the last procedure during the visit.

8 Sample size justification

No formal sample size calculation was performed, as this pilot study does not include a comparative arm. A target sample size of 12 participants was selected, consistent with commonly used sample sizes in feasibility studies.

9 Definitions of patients populations to be analyzed

The **Enrolled set** will consist of all patients who signed informed consent (IC) form.
The **Full analysis set (FAS)**, which will consist of all enrolled participants who received at least one dose of KET01 and who had at least one post-baseline assessment of primary efficacy measurement, will be used for all efficacy endpoints and analyses.
The **Safety set (SAF)** will consist of all enrolled participants who received at least one dose of KET01.
The **Per-protocol set (PPS)** will be defined as all subjects who were included into the FAS and had no major protocol deviations that could have an influence on the primary efficacy endpoint.

10 Statistical analyses

10.1 General considerations

For continuous variables, descriptive statistics (number of observations, mean, SD, minimum, median, and maximum) will be presented. Categorical variables will be displayed as counts and percentages of non-missing values in each category. The count of missing observations will be provided in all descriptive tables. Descriptive statistics will be presented by visit, if applicable. Baseline values are defined as the last non-missing measurement prior to the first dose of KET01. Change from baseline will be defined as the difference between post-baseline assessment and the baseline value. Full analysis set will be used for all efficacy analyses, unless specified otherwise. Intercurrent events (ICEs) are events that occur post-dose that may affect the collection or interpretation of data. The intercurrent events to consider in this study are:

- Drug stopped early, drug withheld and recontinued before Visit 7.
- Lost to follow-up/withdrawal before Visit 7.

All potential intercurrent events will be reviewed prior to database lock.

An overview of study visits can be found in Figure 1. Baseline values are defined as results of rating scales measured at visit 3. End of study treatment is at visit 7, and end of study is at visit 9. Visit windows are specified in the "study day" row of Figure 1. Any change of the specified visit day (e.g. unscheduled visits or missing visits), or missing values from any specific outcome measure, will result in the subject's exclusion from the analysis of that specific outcome measure for a certain timepoint.

10.2 Primary efficacy outcome measures

For the primary estimand of the primary and all secondary efficacy endpoints, treatment policy strategy will be applied, to match intention to treat (ITT) analysis. Subjects who stopped early, withheld drug and recontinued will not be excluded from the analysis, so the primary endpoint analysis population will remain the same as the ITT analysis population regardless of these ICEs. Lost to follow-up/withdrawals before Day 8 will lead to missing data for the primary endpoint, however these will be treated as if the data was missing for any other reason, such as a missed visit, and will not be explicitly imputed for the primary analysis. If data is normally distributed, a paired t-test will be applied to compare MADRS at baseline (day 1) and at day 8. Otherwise, related-samples Wilcoxon signed-rank test will be used to investigate changes in symptom severity. Summary statistics for observed values and changes from baseline will be presented by visit.

As a sensitivity analysis, while-on-treatment strategy will be applied for all ICEs, last-observation-carried-forward (LOCF) technique will be applied. The primary endpoint using treatment policy strategy for ICEs will be analyzed in the PPS as supporting analysis as well.

10.3 Secondary efficacy outcome measures

Secondary efficacy endpoints include:

- Change in total MADRS score between baseline (day 1) and day 3, 5, 15 and 29. In MADRS, 10 items are rated with a score of 0 to 6 (total score: 0 to 60). A higher MADRS score indicates more severe depression. Cut-off points: 0 to 6: normal/symptom-free, 7 to 19: mild depression, 20 to 34: moderate depression 35 to 60: severe depression.
- Change in CGI-S from baseline (day 1) to every post-baseline measurement (day 3, 5, 8, 15, 29). In CGI-S, the overall illness severity is rated from 1 to 7:
  1: Normal, not at all ill
  2: Borderline mentally ill
  3: Mildly ill
  4: Moderately ill
  5: Markedly ill
  6: Severely ill
  7: Among the most extremely ill patients
- Total score of CGI-E at every post-baseline measurement (day 3, 5, 8, 15, 29). The CGI-E is rated using a 4 × 4 matrix, consisting of:
  Therapeutic Effect: 1 = Marked; 2 = Moderate; 3 = Minimal; 4 = None
  Side Effects: 1 = None; 2 = Do not significantly interfere with functioning; 3 = Significantly interfere with functioning; 4 = Overwhelming and intolerable.

The CGI-E result is recorded as a paired score (e.g., 2:1, indicating a moderate therapeutic effect with no adverse effects). Investigators should base their evaluation on all available clinical information, including observed symptom changes, participant-reported outcomes, and the nature and impact of any adverse events.

- Change in PHQ-9 between baseline (day 1), end of treatment (day 8) and the two follow-up visits (day 15 and 29). In PHQ-9, 9 items are rated with a score of 0 to 3 from being experienced never (0) to almost every day (3) during the last 2 weeks (total score: 0 to 27). A higher PHQ-9 score indicates more severe depression. Cut-off points: 0-4: None to minimal depression, 5-9: Mild depression, 10-14: Moderate depression, 15-19: Moderately severe depression, 20-27: Severe depression
- Change in composite inflammatory depressive symptom score (InfDep score) consisting of PHQ-9 items # 3, 4 and 5 between baseline (day 1), end of treatment (day 8) and the two follow-up visits (day 15 and 29).
- Change in GAD-7 between baseline (day 1) and the two follow-up visits (day 15 and 29).
  In GAD-7, 7 items are rated with a score of 0 to 3 from being experienced never (0) to almost every day (3) during the last 2 weeks (total score: 0 to 27). A higher GAD-7 score indicates more severe anxiety. Cut-off points: 0-4: No to low anxiety, 5-9: Mild anxiety, 10-14 Moderate anxiety, 15+ Severe anxiety.
- Response rate (≥ 50% decrease from baseline in MADRS total score) at every post-baseline visit (day 3, 5, 8, 15, 29).
- Remission rate (MADRS score of ≤10) at every post-baseline visit (day 3, 5, 8, 15, 29).
- Change in Sedentary Behaviour (SED), Low-Intensity Physical Activity (LPA) and Moderate- to Vigorous Physical Activity (MVPA) and number of steps, between baseline (day 1) and every post-baseline visit (day 3, 5, 8, 15, 29).
- Change in sleep patterns total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO) and number of awakenings (NA) between baseline (day 1) and every post-baseline visit (day 3, 5, 8, 15, 29).
- Changes in blood plasma levels of the inflammatory biomarkers high-sensitive C-reactive protein (hs-CRP), IL-6, tumor necrosis factor alpha (TNF-α) and WBC count between baseline (day 1) and three post-baseline visits (day 8, 15, 29).
- Change in DNA methylation patterns between baseline (day 1) and two post-baseline visits (day 8 and day 29).
- Change in CD-RISC-25 between baseline (day 1) and two post-baseline visits (day 8 and 29). In CD-RISC-25, 25 statements are rated with a score of 0 to 4 from being not true at all (0) to true almost all the time (4) (total score: 0 to 100). A higher CD-RISC-25 score indicates higher resilience.

Treatment policy strategy will be applied for secondary endpoints. All continuous secondary efficacy endpoints will be analyzed with paired t-tests if normally distributed, otherwise related-samples Wilcoxon signed-rank test will be used. In an exploratory manner, summary tables will be presented by visit. Observed values and changes from baseline to post-baseline visits of continuous endpoints will be summarized using descriptive statistics in order to visualize the data in a clear way, for example using standard deviations or interquartile ranges depending on distributional properties. Only depressive symptoms rated with MADRS (the primary objective) will be transformed into a categorical endpoint where response is defined as MADRS reduction of 50 % and remission is defined as MADRS score < 10 points. To test the hypothesis if MADRS treatment response is associated with increased levels of inflammatory markers, levels of inflammatory markers in subjects who meet criteria for response or remission and those who do not will be compared using T-tests or Wilcoxon signed-rank test (depending on distributional properties). The overall improvement in all subjects will also be related to change in inflammatory markers in an exploratory way, e.g. by correlation analyses.

A post hoc analysis of placebo arms from adjunctive treatment trials in major depressive disorder may be conducted to provide context for the findings of this study; however, this would not constitute a formal comparison.

Additionally, disposition, demographic and other baseline data will be presented using Enrolled set, and Safety set. Treatment duration and compliance will be summarized using Full analysis set and Safety set.

10.4 Safety analyses

All safety assessments will be considered exploratory and will be summarized using the Safety set.

Adverse Events

All AEs will be summarized according to system organ class (SOC) and preferred term (PT) assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA; highest version). An event that emerges during treatment having been absent prior to treatment or worsens relative to the pre-treatment state is defined as a Treatment Emergent Adverse Events (TEAE). In this clinical trial all AEs with onset or worsening after first intake of IMP until 14 days after last intake of IP are defined as treatment emergent. Number and percentage of participants from the Safety set who experienced any treatment emergent adverse events (TEAEs) will be displayed. Furthermore, TEAEs will be summarized by seriousness, relatedness and maximum severity. Any serious TEAEs, TEAEs of Special Interest (AESI) and/or TEAEs that led to withdrawal will be listed.For definitions of adverse reactions (AR), serious adverse reactions (SUSAR) and AESI please see the study protocol.

C-SSRS

Columbia-Suicide Severity Rating Scale (C-SSRS) data will be summarized using counts and percentages by visit. In C-SSRS, suicidality is mapped by yes/no questions and rating scales from 1 to 5. The higher the score on these scales, the more severe is the suicidality. The suicidal ideation score will be summarized by visit.

Other Safety Assessments

Clinical safety laboratory assessments will include biochemistry, haematology, urinalysis, and lipid panels. A urine pregnancy test will be performed for women of childbearing potential. These assessments are primarily conducted to determine eligibility and to monitor participant safety during the study.

Additional safety assessments will include vital signs, physical examinations, and ECG recordings. These data will be summarized descriptively for internal monitoring and safety evaluation only and are not planned for inclusion in scientific publications.

All laboratory data will be presented by visit, displaying the actual values and changes from baseline, where applicable. Shift tables for values outside the normal ranges will be presented, as appropriate. Other safety data include vital signs assessments, physical examinations, and ECG findings. These results will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

11 Statistical program

R or IBM SPSS Statistics 28 or higher Windows (IBM Corporation, Armonk, NY, USA), SAS Enterprise Guide 8.3 for Windows (SAS Institute Inc., Cary, NC, USA) will be used for the statistical analyses.