SAP – Statistical Analysis Plan

for

Cannabidiol for treatment of non-affective psychosis and cannabis use

Statistical Analysis Plan (SAP)
Trial: *Cannabidiol for treatment of non-affective psychosis and cannabis use*
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List of Abbreviations

AE – Adverse Event
ANCOVA – Analysis of Covariance
BACS – Brief Assessment of Cognition in Schizophrenia
CBD – Cannabidiol
CGI-I – Clinical Global Impressions – Improvement scale
CGI-S – Clinical Global Impressions – Severity scale
CONSORT – Consolidated Standards of Reporting Trials
ECG – Electrocardiogram
GLM – General Linear Model
IQR – Interquartile Range
LLOQ – Lower Limit of Quantification
LOCF – Last Observation Carried Forward
MAR – Missing At Random
MedDRA – Medical Dictionary for Regulatory Activities
MICE – Multiple Imputation by Chained Equations
MIREDIF – Minimum Relevant Difference
MMRM – Mixed-Effects Model for Repeated Measures
MNAR – Missing Not At Random
PANSS – Positive and Negative Syndrome Scale
PSP – Personal and Social Performance scale
QTc – Corrected QT interval
SAE – Serious Adverse Event
SAP – Statistical Analysis Plan
SD – Standard Deviation
SWN-S – Subjective Well-being under Neuroleptic treatment Scale
THC – Tetrahydrocannabinol
UN – Unstructured (covariance structure)
UKU – Udvalget for Kliniske Undersøgelser (UKU Side Effect Rating Scale)

1. Objectives, endpoints and estimands

To investigate the effect of cannabidiol (CBD) for the treatment of non-affective psychosis, including schizophrenia, in patients with a current or past history of cannabis use. The effect of CBD will be assessed primarily with respect to psychotic symptoms, and secondarily with respect to cannabis use and a range of other clinically relevant symptom and functional domains.

- **Population:** All randomized patients fulfilling inclusion/exclusion criteria, as stated in the protocol.
- **Treatment:** 7 weeks of CBD 600 mg/day vs. risperidone 4 mg/day, both as monotherapy with double-dummy design.

1.1 Primary Endpoint

- **Change from baseline to week 7 on the Positive and Negative Syndrome Scale (PANSS) Positive subscale**

1.2 Secondary Endpoints

- **Symptom response**
  - Response categories: 1–24%, 25–49%, 50–74%, 75–100% reduction (Leucht et al., 2010)
  - The lowest score is 30 which is equivalent to 'no symptoms'. When calculating the percentage reduction from baseline, we will, according to Leucht et al 2010 (Leucht et al., 2010), subtract the 30 points from the scores, to avoid an underestimation of the effect
- **Clinical Global Impressions – Improvement (CGI-I) at week 7**
- **Personal and Social Performance (PSP) change from baseline to week 7**
- **Subjective well-being (SWN-S) change from baseline to week 7**
- **Brief Assessment of Cognition in Schizophrenia (BACS) composite and domain scores, change from baseline to week 7**
- **Symptom remission**
  - Remission as a dichotomous outcome: Yes, if PANSS score ≤3 on P1, P2, P3, N1, N4, N6, G5 and G9 (Andreasen et al., 2005, duration criterion not applied)

- **Cannabis use pattern change from baseline to week 7**
  - Self-reported days/week
    - Only patients with a current use at baseline are included
  - Quantity (PSYSCAN items #6-8).
    - Only patients with a current use at baseline are included.

1.3 Exploratory Endpoints

- **Sleep and circadian measures change from baseline to week 7**
  - Actigraphy
  - Polysomnography
  - Subjective sleep quality:
    - Pittsburgh Sleep Quality Index

- **Cannabis cessation at week 7**
  - Cannabis cessation, self-report, no use in past 2 weeks at week 7.
    - Only patients with a current cannabis use at baseline are included.
  - Cannabis cessation, plasma tetrahydrocannabinol (THC) negative.
    - Only patients with a current cannabis use at baseline are included.

- **Metabolomics**
  - Exploratory analysis of metabolomics will be performed by Retskemisk Institut.

1.4 Safety Endpoints

- **Adverse events**
  - Safety analyses will be conducted in the safety population, defined as all participants who received at least one dose of study medication. Adverse events (AEs were actively solicited at all study visits through clinician inquiry and clinical assessment but were not collected using a formal structured adverse event instrument. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarised descriptively by treatment group (Junqueira et al., 2023).

- **Discontinuation due to adverse events/serious adverse events (SAEs)**

- **UKU - Udvalget for Kliniske Undersøgelser – Change from baseline to week 7**
  - In addition to adverse events recorded at each study visit, side effects were systematically assessed at baseline and at week 7 using the UKU Side Effect Rating Scale, which provides a structured and standardized evaluation of potential treatment-emergent side effects.
- **Other safety measures:**
  - Changes from baseline to week 7 in body weight, prolactin, lipid profile, and liver function.
    Changes from baseline to week 7 in electrocardiographic (ECG) parameters, including the QTc interval.

2. Study design

Randomized, double-blind double-dummy, parallel group, 1:1 allocation to CBD vs. risperidone, 7-week treatment plus 2-week safety visit. Clinical assessments at baseline and weeks 1, 3, 5, 7 and telephone assessments in weeks 2, 4, 6.

3. General statistical principles

- Two-sided $\alpha = 0.05$ for primary endpoint.
- 95% confidence intervals for treatment effects.
- Multiplicity adjustment: A prespecified stepwise hierarchical testing procedure will be applied to the secondary endpoints to control the overall family-wise type I error rate at 0.05 (two-sided).
- Continuous variables: mean (SD) or median (IQR); categorical: n (%).
- Main analyses in R Studio - version 4.5.0 (2025-04-11 ucrt)

4. Sample size calculation

We consider an improvement of 4 points (delta) on the PANSS positive subscale is of minimum clinical relevance (MIREDIF). Leucht et al. defined a clinically meaningful change on the PANSS total scale to be 15 points (Leucht et al., 2006). Extrapolating this to the positive subscale yields an improvement of 4 (15/30 x7) points (delta) on the PANSS positive subscale as the MIREDIF. We assume that the PANSS positive score is approximately normally distributed in both treatment groups with a standard deviation (sigma) of 5 points (Leweke et al., 2012). This yields a sample of 25 patients in each group with a two tailed 5% significance level and 80% power. Subjects will be randomized in a 1:1 ratio to each intervention group.

We expect a drop-out rate between 20 % and 30 % (Kemmler et al., 2005) and thus we reckon that N=64 must be included in the study.

5. Unblinding and timing of analyses

No analyses were conducted prior to finalisation of this Statistical Analysis Plan (SAP). Following approval of the SAP and its upload to ClinicalTrials.gov, the unblinding process will be performed in a stepwise manner.

Initially, participants will be assigned to Group 1 and Group 2 without disclosure of the actual treatment allocation. To preserve blinding as long as possible, one participant who was unblinded during the conduct of the trial will remain excluded from all analyses until final unblinding.

Primary efficacy analyses will be conducted, and primary conclusions will be finalised while treatment allocation remains blinded. Full unblinding will occur only after completion and documentation of the primary analyses. Secondary and exploratory analyses may not be fully completed prior to unblinding.

6. Statistical analyses

The primary outcome will be analysed using a mixed-effects model for repeated measures (MMRM) under the missing-at-random (MAR) assumption, with an unstructured covariance matrix for the within-subject repeated measures

The primary covariance structure for the MMRM analysis will be unstructured (UN), which allows for maximum flexibility in modelling the correlations between repeated measurements within subjects. If the model with UN covariance structure fails to converge, alternative covariance structures will be tested in the following order until convergence is achieved:

1. Heterogenous auto-regressive order 1
2. Heterogeneous compound symmetry
3. Homogeneous auto-regressive order 1
4. Homogeneous compound symmetry

The selected covariance structure will be reported in the analysis results. Model selection will be based on successful convergence.

To assess the robustness of the primary MMRM results under the MAR assumptions to alternative assumptions regarding missing data, sensitivity analyses will be conducted as recommended by Consolidated Standards of Reporting Trials (CONSORT) (Hopewell et al., 2025).

- First, a complete-case ANCOVA will be conducted using Week-7 PANSS Positive score as the dependent variable, adjusting for baseline PANSS Positive score, sex and age.
- Second, a missing-not-at-random (MNAR) sensitivity analysis will be implemented using delta-adjustment defined as increasing proportions of the observed treatment effect from the primary MMRM analysis (delta = 0%, 10%, 20%, 30%, 40%, and 50%). A delta value of 0%

corresponds to the MAR assumption, whereas delta values greater than 0% represent departures from MAR by assuming systematically worse outcomes among participants with missing data. Treatment effects will be re-estimated under each scenario, and the robustness of the primary conclusion will be evaluated based on the size of delta required to alter the interpretation of the primary analysis (tipping-point assessment).

6.1 Primary endpoint analysis

- **Change from baseline to week 7 on the PANSS Positive subscale**
    - The primary outcome is the change in PANSS Positive subscale score from baseline to week 7. This will be analysed using a MMRM, as described above. The model will include fixed effects for treatment group, visit, and the treatment-by-visit interaction, with adjustment for baseline PANSS Positive score sex and age as covariates.
    - **Sensitivity analyses**
        - Complete-case ANCOVA of Week-7 PANSS Positive adjusting for baseline PANSS Positive, sex and age.
        - MNAR sensitivity analysis using delta-adjustment (delta = 0%, 10%, 20%, 30%, 40%, and 50%) followed by the same ANCOVA model.
    - **Effect-modification analyses**
        - Prespecified subgroup analyses will be conducted to assess potential effect modification by baseline characteristics by testing treatment-by-subgroup interaction terms within the MMRM framework. The following subgroups will be evaluated: (a) sex (male vs female; treatment-by-sex interaction) and (b) current cannabis use at baseline (yes vs no; treatment-by-cannabis use interaction).

6.2 Secondary endpoints analyses

Hierarchical testing strategy for secondary endpoints:
To control the overall family-wise type I error rate at a two-sided alpha level of 0.05, secondary endpoints will be tested using a prespecified stepwise hierarchical (fixed-sequence) testing procedure. Testing will proceed in the order specified below. Formal statistical significance will be claimed only for endpoints tested prior to the first non-significant result ($p \geq 0.05$). Endpoints tested after failure of the hierarchy will be analysed and reported; however, corresponding p-values will be considered nominal and interpreted descriptively.
Hierarchical testing order:

1. Symptom response
2. CGI-I
3. PSP
4. SWN-S
5. BACS
6. Symptom remission
7. Cannabis use pattern

- **Symptom response:**
  - **Response:** Ordinal treatment response categories measured at each post-baseline visit will be analysed using an ordinal mixed-effects model with treatment group, visit and their interaction as fixed effects, adjusting for baseline total PANSS score sex and age. A random subject effect will be included to account for repeated measurements.
  - **Effect-modification analyses**
    - Prespecified subgroup analyses will be conducted to assess potential effect modification by baseline characteristics by testing treatment-by-subgroup interaction terms within the MMRM framework. The following subgroups will be evaluated: (a) sex (male vs female; treatment-by-sex interaction) and (b) current cannabis use at baseline (yes vs no; treatment-by-cannabis use interaction).

- **CGI-I**
  - **Outcome:** Ordinal improvement scale with 5 ordered categories (for CGI-I: “much improved”, “improved”, “no change”, “worsened”, “much worsened”).
  - **Model:** CGI-I outcomes will be analysed using mixed-effects ordinal logistic regression models incorporating repeated assessments at Weeks 1, 2, 3, 4, 5, 6 and 7. Models will include fixed effects for treatment group, visit, sex, age, baseline CGI-S score, and the treatment-by-visit interaction. A random intercept for participants will be included to account for within-subject correlation.
  - **Descriptive summaries:** For each visit (Weeks 1–7), the distribution of CGI-I categories will be summarised descriptively by treatment group as counts and percentages (n, %).
  - **Missing data:** Model estimation will be performed under the MAR assumption using all available post-baseline observations.
  - **Effect modification analyses:**
    - Prespecified subgroup analyses will be conducted to assess potential effect modification by baseline characteristics by testing treatment-by-subgroup interaction terms within the MMRM framework. The following subgroups will be evaluated: (a) sex (male vs female; treatment-by-sex interaction) and (b) current cannabis use at baseline (yes vs no; treatment-by-cannabis use interaction).

- **PSP, SWN-S, BACS**
  - Continuous scores (PSP, SWN-S, BACS composite and domain scores):
  - **Outcome:** Change from baseline to week 7
  - **Model:** ANCOVA with the Week-7 score as the dependent variable, treatment group as a fixed effect, and baseline score of the respective outcome, sex and age included as covariates. Adjusted mean differences between treatment groups will be reported with 95% confidence intervals.
  - **Missing data:** Participants with missing Week-data will be excluded from the analysis; no imputation will be performed for this outcome.

- **Effect modification analyses:**
  - Pre-specified subgroup analyses will be conducted to explore potential effect modification by 1) sex (male vs female) and 2) current cannabis use at baseline (yes vs no). Subgroup effects will be evaluated by including treatment-by-subgroup interaction terms in the ANCOVA models.

- **Cannabis use pattern**
  - Only participants with a current use of cannabis at baseline are included.
  - **Outcome**: number of days/week and grams/week of cannabis use.
  - **Model**: These outcomes will be analysed using MMRM at Weeks 1, 3, 5, and 7, including fixed effects for treatment group, visit, and the treatment-by-visit interaction, sex, age, and adjusted for baseline cannabis use.
  - **Missing data:** All available post-baseline observations will contribute to the analysis under the MAR assumption.
  - **Effect modification analyses:**
    - Prespecified subgroup analyses will be conducted to assess potential effect modification by baseline characteristics by testing treatment-by-subgroup interaction terms within the MMRM framework. The following subgroups will be evaluated: (a) sex (male vs female; treatment-by-sex interaction) and (b) current cannabis use at baseline (yes vs no; treatment-by-cannabis use interaction).

- **Symptom remission:**
  - **Remission:** Remission status (yes/no) at Week 7 will be analysed using logistic regression with treatment group as the primary predictor and adjustment for baseline total PANSS, sex and age as covariates.
    - **Missing data:** Remission requires Week-7 PANSS item data. If Week-7 PANSS items required to derive remission are missing, missing values will be handled under the MAR assumption using multiple imputation. Remission status will then be derived from the imputed Week-7 PANSS item scores.
  - **Effect modification analyses:**
    - Pre-specified subgroup analyses will be conducted to assess potential effect modification by sex (male vs female) and current cannabis use at baseline (yes vs no). Subgroup effects will be evaluated by including treatment-by-subgroup interaction terms in the respective regression models.

- **Adherence:**
  - Treatment adherence will be assessed using both pill counts and plasma drug concentrations.
  - Pill count adherence will be calculated as the percentage of prescribed doses taken, based on the difference between dispensed and returned study medication. Pill count adherence will be summarised as a continuous measure (percentage adherence) by treatment group. Pill count adherence will be calculated only for participants with returned study medication available at end

of treatment (or at early discontinuation). If returned study medication is not available, pill count adherence will be considered missing
- Non-adherence will be categorized dichotomously, as detectable versus non-detectable plasma concentrations. This will be based on the assay's lower limit of quantification (LLOQ).
- Plasma drug concentrations will be analysed as continuous measures and summarised descriptively by treatment group using appropriate summary statistics.
- Adherence measures will be reported descriptively by treatment group. As adherence is a post-randomisation variable, no formal hypothesis testing is planned.

6.3 Exploratory endpoint analysis

- **Cannabis cessation**
  - Following the revision of the eligibility criteria and the reclassification of cannabis cessation from a primary to a secondary outcome, this endpoint is considered exploratory. As the original sample size calculation was based on this outcome, the study may be underpowered to detect statistically significant differences for this endpoint.
  - Only participants with a current cannabis use at baseline will be included.
  - **Outcome**:
    - Cessation (yes/no) at week 7, self-reported.
    - Cessation (yes/no) at week 7, Plasma THC (present/not present)
  - **Model**: logistic regression with treatment group as main predictor, adjusting for age, sex, baseline days/week of cannabis use and baseline quantity.
  - **Missing data:** Participants with missing Week-7 cessation status will be excluded from the primary analysis; no imputation will be performed for this exploratory outcome.
  - **Subgroup analyses**
    - Sex differences will be assessed by including a treatment-by-sex interaction term in the logistic regression model.

- **Sleep and circadian measures**:
  - Supplementary SAP for the sleep variables will be developed later, prior to the analysis of these outcomes

- **Metabolomics**
  - Supplementary SAP for the metabolomics will be developed later, prior to the analysis of these outcomes

6.4 Safety endpoints analyses

- **Adverse events**
  - Safety summaries will include the number and percentage of participants experiencing at least one adverse event, serious adverse events (SAEs), treatment-related adverse events, and adverse events leading to treatment discontinuation.
  - Discontinuation due to adverse events/SAEs
  - Adverse events will be presented by system organ class and preferred term. No formal hypothesis testing is planned for comparisons of adverse event rates between treatment groups, and all safety analyses will be considered descriptive.

- **UKU Udvalget for Kliniske Undersøgelser**
  - Provides a systematic and structured assessment of potential treatment-emergent side effects. UKU total scores (and subscale scores, e.g. extrapyramidal side effects) will be summarised descriptively by treatment group at baseline and at Week 7.
  - Between-group differences in UKU scores at Week 7 will be explored using ANCOVA, with the Week-7 UKU score as the dependent variable, treatment group as a fixed effect, and baseline UKU score, sex and age included as a covariates. Results will be reported as adjusted mean differences with 95% confidence intervals.
  - Participants with missing Week-7 UKU assessments will be excluded from the UKU analysis, and the extent of missing data will be reported.

- **Other safety measures:**
  - Changes from baseline in prolactin, lipid profile, and liver function tests will be summarised by treatment group using mean change from baseline with 95% confidence intervals. Between-group differences at Week 7 will be explored using analysis of covariance (ANCOVA) with adjustment for baseline values, sex and age.
  - Changes in body weight will be analysed using an MMRM including weight measurements at Weeks 3 and 7, with fixed effects for treatment group, visit, and treatment-by-visit interaction, and adjustment for baseline weight, sex and age.
  - ECG parameters, including QTc interval, will be summarised descriptively by treatment group. The number and proportion of participants exceeding prespecified clinically relevant thresholds will be reported.

6.5 Descriptive statistics

Baseline characteristics will be descriptively summarized, within each of the two groups randomised to either CBD or risperidone.
The list of baseline variables to be summarized includes:

- Age
- Sex
- Race
- Diagnosis

- PANSS positive and total
- CGI-S
- Use of cannabis
- Living situation
- Marital status
- Educational level
- Employment status

Continuous variables will be summarised using means and standard deviations for approximately normally distributed data, and medians with interquartile ranges for skewed distributions. Categorical variables (e.g., living situation, marital status, education level, and employment status) will be presented as counts and percentages. No statistical tests will be performed for baseline comparisons, in accordance with CONSORT recommendations(Hopewell et al., 2025).

6.6 Modifications from protocol-planned analyses

The protocol, originally conceived of in 2018, and published in 2021 (Rasmussen et al., 2021), prespecified the use of a univariate general linear model with the primary endpoint as the dependent variable, applying last observation carried forward (LOCF) for missing data and including treatment group, age, and baseline values as covariates. While this approach was consistent with common practice at the time, methodological standards for the analysis of longitudinal clinical trial data have evolved since then.

Mixed-effects models for repeated measures are now widely regarded as the preferred analytic framework for continuous longitudinal outcomes in clinical trials(Hopewell et al., 2025; Mallinckrodt et al., 2003). MMRM provides several advantages over LOCF-based approaches: it uses all available data across time points without imputing missing values, relies on less restrictive assumptions than LOCF, accommodates individual variability in outcome trajectories, and yields unbiased estimates under the missing-at-random assumption(Hopewell et al., 2025; Mallinckrodt et al., 2003). Moreover, MMRM aligns with contemporary regulatory guidance and enhances statistical efficiency by modelling within-subject correlations directly.

For these reasons, the primary analysis will be conducted using an MMRM approach rather than the originally planned univariate GLM with LOCF. This change improves methodological rigor while remaining consistent with the scientific aims and data structure specified in the original protocol.

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