Adjunctive treatment with Pramipexole for Anhedonia Symptoms of Depression

PRIME-PRAXOL

Statistical Analysis Plan (SAP)

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1 Table of contents

2 Roles and responsibilities

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Name: Filip Ventorp

Role: co-PI

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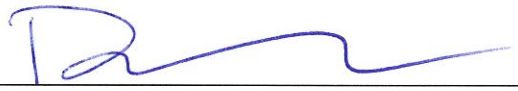
Role: Statistician

Organization: Clinical Studies Sweden, Forum South

3 Signature

We have read this Statistical Analysis Plan carefully and believe that it contains all the necessary information to carry out the analyses of the PRIME-PRAXOL study.



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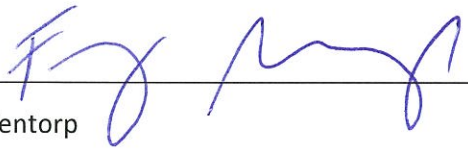

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4 Introduction

The majority of depressed patients do not achieve remission with current methods. A common and disabling symptom after treatment is anhedonia – the inability to fell pleasure and reduced "drive". Today, there is no specific and effective treatment method for anhedonia. Pramipexole is a dopamine agonist used in Parkinson's disease and has been shown in several clinical studies to be effective against anhedonia symptoms in this disease. Clinical experience has shown a treatment effect with high-dose pramipexole in treatment-refractory depression, but randomized clinical studies have only been conducted with low-dose pramipexole and have not investigated the specific effects against anhedonia. In a recently completed pilot study from our research group, approximately one third of patients showed a treatment effect on high dose pramipexole.

The purpose of this study is to investigate the effect of add-on pramipexole on anhedonia depression and other symptoms in patients with depressive disorders.

The SAP covers the primary and some of the secondary efficacy variables.

For detailed information, see the Protocol which has been pre-published (*1*)

5 Objectives and issues

The overall objective is to investigate the efficacy and tolerability of add-on pramipexole in anhedonia depression.

Biomarkers have been collected for a subset of the patients to demonstrate target engagement and find treatment predictors.

6 Study design

6.1 Study design

This is a double-blind trial in which a total of 80 patients are randomized to receive either add-on pramipexole or placebo for nine weeks. Study participants undergo optional fMRI examination and lumbar puncture at baseline and at the end of the RCT.

For detailed information, see the pre-published Protocol (*1*).

6.2 Sample size calculation

For the primary question (SHAPS), a linear mixed model with repeated measures (w 3, w 6 and w 9) will be used, where the primary question will be answered with the overall comparison between the

randomized groups. Any group differences at baseline are corrected by including the baseline values as a covariate in the model. The estimated effect size of pramipexole treatment is estimated at 0.27 as this has been reported in other studies of antidepressant drugs. This corresponds to a score difference in MADRS of approximately 4 points which is considered a clear clinical improvement and corresponds to ≥ 4 points on SHAPS. Estimate of the correlation coefficient between repeated measures of MADRS scores is based on material from our previous pilot study (r=0.5). In a power calculation with strength of 80% and α=0.05, 74 research subjects were estimated to be needed. In the original power calculation, the number of dropouts was estimated to be less than 5% (based on the pilot study), whereby we needed to include 80 research subjects in the study (ITT)

After a planned interim analysis, conducted by an external statistician, we estimate that we need to include 80 patients who reach the week 9 visit (end of study).

6.3 Randomization

The randomization process uses a randomization list generated by an independent statistician at Clinical Studies Sweden – Forum South. Blinded study personnel are unaware of the randomization outcome. Research participants are included/randomized consecutively as they are deemed eligible for the study.

6.4 Interim analysis

An interim analysis was planned according to the original protocol. In June of 2024 an independent statistician conducted an interim analysis on the primary outcome and number of dropouts. The result of this interim analysis was that we decided to increase the number of recruited patients to 80 with complete efficacy data through the week 9 visit.

7 Analysis sets

Primary and secondary outcome measures related to the efficacy of pramipexole will be analyzed in the intention-to-treat (ITT)-population, which is all randomized patients with at least one follow-up assessment, i.e. all patients who reached the week 3 assessment.

We will conduct two separate ITT-analyses:

1. In the event of missing measurements at different time points, we will compensate by using the last observation carried forward (LOCF) method.
2. One analyses with no imputed values

One subject (PP02) was randomized, but it was later noted by the external monitor that he had not fulfilled the SHAPS inclusion criteria. Data from this patient will not be included in the statistical

analyses for the primary and efficacy-based secondary outcomes. This decision was made by the external monitor, lead statistician, and the data manager – none of them involved in assessments of study subject.

The safety population is defined as all patients who received the medication, i.e. adverse events will be reported for all patients who received at least one dose of pramipexole or placebo

8 Outcome measures

8.1 Primary efficacy outcome measures

The primary efficacy outcome measure is the absolute change in the SHAPS (*2*) between baseline and week 9.

8.2 Secondary efficacy outcome measures

The secondary efficacy outcome measure are

- Core depression symptoms (HDRS-6 (*3*))
- Anhedonia (DARS (*4*), covering additional anhedonia domains compared to the SHAPS)
- General depressive symptoms (MADRS-S (*5*))
- Sleep disturbances (ISI (*6*))
- Apathy symptoms (AES (*7*))
- Anxiety symptoms (GAD-7 (*8*))
- Quality of life (BBQ (*9*))

8.3 Additional outcomes measures

Additional outcomes are

- accelerometry
- fMRI

8.4 Safety outcome measure

Adverse events

9 Data processing

9.1 Missing values

If clinical efficacy measurement values are missing at different times, this will be compensated for with last-observation-carried-forward (LOCF).

For the mechanistic secondary outcomes (e.g. fMRI), analyses will be performed only on those subjects who have the necessary data available for these specific analyses, meaning that no imputation will be applied.

9.2 Calculated variables

Total score of the SHAPS will be calculated by summarizing each item with a value from 1 to 4 (max score 56). Total score on the other rating scales will be calculated according to the instructions for each scale.

9.3 Transformations

If assumptions regarding normal distribution are not met, variables may be transformed.

10 Statistical analysis

10.1 Statistical basis

Descriptive statistics will be given as mean (SD), median (Q1–Q3) and (Min–Max) for continuous variables. The number of observations will also be given.
The randomization groups will be compared. Two-sided test of statistical significance is to be used, and the chosen significance level is 0.05. No adjustment for multiplicity will be made.

10.2 Effect

10.2.1 Primary

To answer the primary question, a linear mixed model with repeated measures is used with severity of anhedonia symptoms (SHAPS total score) as the dependent variable and time (week), treatment (pramipexole or placebo), and the interaction of time by treatment as independent variables. The

SHAPS total score at baseline will be used as a covariate in the model. In the event of missing measurements at different time points, this will be compensated for with last observation carried forward (LOCF). Normal distribution is expected based on previous studies.

10.2.2 Secondary

The same statistical method and model as above is used for the other secondary outcome measures where there are more than two measurement points

In addition to analyzing total scores as continuous variables, we will also do descriptive analyses of treatment response and remission status. For this purpose, we use established cut-offs. Response according to the SHAPS is defined as an improvement of ≥50% on total score (each item rated from 1-4), and remission as a SHAPS score of ≤2, based on an alternative scoring approach in which each item is rated either 0 or 1 (*10, 11*). Initially, the published protocol defined SHAPS remission as a score of ≤3. However, to maintain consistency with the original Snaith et al. publication *(12)* — the basis of our SHAPS inclusion criteria — we've updated the definition to a score of ≤2. This was done before all data had been collected and before the randomization code was broken.

Response on the MADRS is defined as ≥50% improvement and remission as a score ≤10. Fisher's Exact test will be used to compare dichotomous outcomes.

10.3 Additional

fMRI experimental designs and planned analysis as well as accelerometry analysis are described in the Protocol (*1*).

10.4 Safety

Adverse events will be presented within randomization groups.

11 Statistical program

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) or R will be used for the statistical analyses. A p-value below 0.05 was considered significant.

12 References

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