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A Randomized, Sham-Controlled Study of PEAR-004 as an adjunct to standard-of-care treatment to schizophrenia

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The reporting and analysis plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CPEA001A12201*".**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP was created using the clinical trial protocol (version 1) dated 12-Oct-2018.

1.3 Study objectives

1.3.1 Primary objectives

Primary objectives	Endpoints related to the primary objectives
• To assess the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce symptoms of schizophrenia. • To evaluate retention to assigned study treatment.	• Change in total PANSS score from baseline to day 85 or last visit. • Percent dropout rate.

1.3.2 Secondary objectives

Secondary objectives	Endpoints related to the secondary objectives
• To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce positive symptoms of schizophrenia • To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce negative symptoms of schizophrenia. • To assess safety and tolerability of PEAR-004. • To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to improve psychosocial functioning in patients with schizophrenia. • To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce	• Change in the Positive PANSS score from baseline to day 29, day 57, and day 85 or last visit. • Change in the General Psychopathology PANSS score from baseline to day 29, day 57 and day 85 or last visit. • Change in the Negative PANSS score from baseline to day 29, day 57, and day 85 or last visit. • Change in the Motivation and Pleasure self-report (MAP-SR) score from baseline to day 29, day 57, and day 85 or last visit. • Adverse events, serious adverse events, and adverse events leading to discontinuation throughout the study.

depression symptoms in patients with schizophrenia. • To evaluate the magnitude of the effect of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce symptoms of schizophrenia. • To evaluate the response to treatment. • To evaluate patient adherence to antipsychotic medication.	• Vital signs at baseline, day 85 or last visit. • InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus) score at baseline, day 29, day 57, day 85, and day 115 or last visit. • Change on the World Health Organization Quality of Life (WHOQOLBREF) scale from baseline to day 29, day 57, and day 85 or last visit. • Change in the Beck Depression Inventory, Second Edition (BDI-II) total score from baseline to day 29, day 57, and day 85 or last visit. • Percentage change in PANSS score (within assigned group) from baseline to day 29, day 57, and day 85 or last visit. • Proportion of responders, defined as a reduction of at least 20% at day 85 or last visit in total PANSS score relative to baseline. • Change in antipsychotic pharmacotherapy use as measured by the Brief Medication Questionnaire (BMQ) at day 29, day 57, and day 85 or last visit.

1.3.3 Exploratory objectives

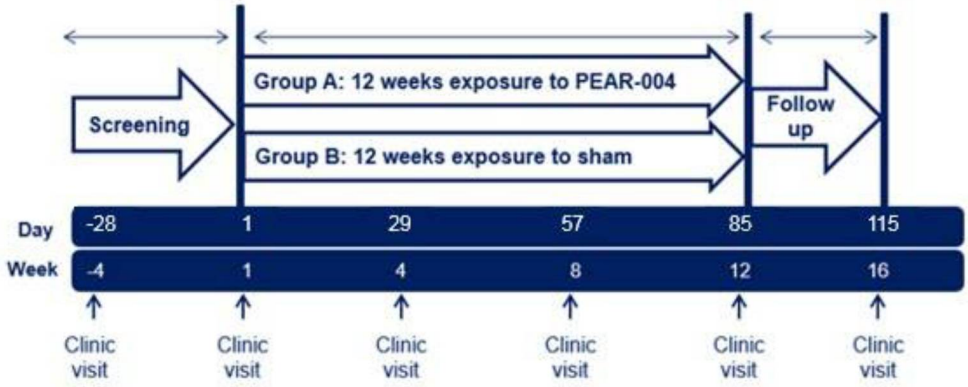
1.4 Study design and treatment

This is a randomized, sham controlled, rater blinded, parallel group design. Approximately 102 subjects will be randomized (with a ratio 1:1) in the following groups:

- Group A: Clinician-directed pharmacotherapy + PEAR-004.
- Group B: Clinical directed pharmacotherapy + Sham application.

An up to 28-day screening period will include standard screening assessments as defined in the assessment schedule. Eligible subjects will be randomized on day 1 into one of the treatment groups. Subjects in both groups will continue to receive their clinician-directed standard of care treatment for schizophrenia, including pharmacotherapy. Subjects in Group A will use PEAR-004 for a period of 12 weeks. Subjects in Group B will use a sham for a period of 12 weeks. Subjects will return to the clinic for outpatient visits at week 4 (day 29), week 8 (day 57), and week 12 (day 85). At each visit, standard assessments will be performed according to the assessment schedule, including PANSS, ISST-Plus, CGI, BMQ, MAP-SR, WHOQOL-BREF, BDI-II, ISI, and Adverse Events (AEs). A final follow-up visit will be performed at week 16 (day 115), including the assessments as detailed in the assessment schedule. A graphical description of the described procedure is presented in Figure 1-1.

Figure 1-1. Study design



2 First interpretable results (FIR)

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3 Interim analyses

Interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. In this case, the analyses as described in the sections below are conducted for the relevant endpoints.

4 Statistical methods: Analysis sets

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this trial. The FAS comprises all subjects to whom study treatment has been assigned by randomization and who have a baseline observation and at least one post-randomization observation for the analysis endpoint. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. The baseline is defined as the last measurement obtained before administration of the randomized treatment intervention (PEAR-004/Sham) on Day 1.

The Safety Set includes all randomized subjects who received the study treatment, with subjects included in the treatment group corresponding to the treatment they actually received. While no per-protocol analysis is planned, a list of protocol violators (e.g. subjects with lack of study treatment compliance change in background therapy during the trial) will be finalized prior to analysis.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
COMD01	Data from the subjects acquired after this protocol deviation will be excluded from the analysis.	-

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

Not applicable.

6 Statistical methods for efficacy parameters

6.1 Primary objective

The primary efficacy endpoint in the study is change in total PANSS score from baseline to day 85 or last visit, analyzed using the FAS.

6.1.1 Variables

PANSS score.

6.1.2 Statistical model, assumptions, hypotheses and method of analysis

The change from baseline in total PANSS score will be analyzed using the mixed-effects model for repeated measures (MMRM) (see Mallinckrodt et al (2001)), including the fixed, categorical effects of treatment, visit (i.e., day 1, 29, 57, 85), and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score, baseline score-by-visit interaction, and disease duration at baseline. An unstructured (UN) covariance structure will be used to model the within-patient errors. The Kenward-Roger (KR) method will be used to adjust the estimated covariance of the mean difference and the degrees of freedom.

6.1.2.1 Model checking procedures

The primary MMRM model implicitly imputes missing data under a missing at random (MAR) assumption. Therefore, no explicit imputation of missing data will be done for the primary analysis approach.

Two sensitivity analyses to assess the robustness of the primary analysis to missing data results will be performed.

6.1.2.2 Graphical presentation of results

Because there is a temporal component throughout the data, individual plots and model adjusted mean and 95% CIs plot showing the change from baseline over time will be presented.

6.2 Secondary objectives

The secondary efficacy endpoints listed below will be analyzed separately using an MMRM analysis. The model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score, baseline score-by-visit interaction, and disease duration at baseline (in years).

6.2.1 Variables

The change from baseline to each post-baseline visit, which will be the dependent variable.

6.2.2 Statistical methods for analysis

The analysis strategy will be the same as for the primary outcome. The outcomes to be analyzed are:

- Change from baseline in the positive PANSS score;
- Change from baseline in the General Psychopathology PANSS score;
- Change from baseline in the negative PANSS score;
- Change from baseline in the MAP-SR score;
- Change from baseline in the WHOQOL-BREF scale;
- Change from baseline in the BDI-II total score.

In addition, the percentage change from baseline in the total PANSS score will be analyzed using an MMRM approach. Estimates of mean percentage change from baseline to each study visit with (95% CIs) will be obtained for each treatment group (i.e., 100*(Post Baseline - Baseline)/Baseline)).

The data from BMQ will be listed and summarized descriptively.

6.2.3 Sensitivity analysis for the primary endpoint

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6.2.3.1 Model checking procedures

The primary MMRM model implicitly imputes missing data under a missing at random (MAR) assumption. Therefore, no explicit imputation of missing data will be done for the primary analysis approach.

6.2.3.2 Graphical presentation of results

Because there is a temporal component throughout the data, individual plots and model adjusted with mean and 95% CIs plot showing the change from baseline over time will be presented.

6.2.4 Supportive analysis for the primary endpoint

The last-observation-carried-forward (LOCF) approach will be applied to analyze the change from baseline in the total PANSS score. These results will only be used to aid in the interpretation of the results from the primary analysis.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for

adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (**treatment-emergent** AEs).

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature) and ISST-PLUS.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions and any other relevant information will be listed by treatment group and subject.

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment and subject.

Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to the study treatment will be summarized using descriptive statistics. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

Reasons for discontinuation for all patients will be listed and tabulated for both treatment groups. The median time to all-cause discontinuation will be compared between the treatment groups. The log-rank test will be used to test the null hypothesis against the alternate hypothesis that the median time to discontinuation is not the same between the groups.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Other safety evaluations

ISST-Plus score data will be listed by treatment, subject and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time as appropriate.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data will be created.

8 Reference list

Mallinckrodt CH, Clark WS, David SR (2001) Accounting for dropout bias using mixed-effects models. *Journal of Biopharmaceutical Statistics*; 11:9-21.