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Clinical Trial Protocol CPEA001A12201

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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
BDI-II	Beck Depression Inventory, Second Edition
BMQ	Brief Medication Questionnaire
CBT	Cognitive Behavioral Therapy
	Corporate Confidential Information
ClinRO	Clinician Reported Outcomes
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
	Corporate Confidential Information
ISMT	Illness Self-Management Training
ISST-Plus	InterSePT Scale for Suicidal Thinking-Plus
MAP-SR	Motivation and Pleasure-Self Report
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effects model for repeated measures
PANSS	Positive and Negative Syndrome Scale
PDT	Prescription Digital Therapeutic
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-5
SD	standard deviation
SST	Social Skills Training
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study treatments prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the treatment being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

Protocol summary

Protocol number	CPEA001A12201
Full Title	A Randomized, Sham-Controlled Study of PEAR-004 as an adjunct to standard-of-care treatment for schizophrenia
Brief title	Study of efficacy of PEAR-004 in schizophrenia
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Device
Study type	Interventional
Purpose and rationale	The purpose of the study is to determine in patients currently being administered antipsychotic pharmacotherapy whether PEAR-004 can further reduce symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS). The overall rationale for the study is to assess the first prescription digital therapeutic (PDT) in schizophrenia using a form of proven psychosocial intervention, cognitive behavioral therapy (CBT), to supplement standard of care with antipsychotic medications.
Primary Objective(s)	The primary objectives are to assess the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce symptoms of schizophrenia by change in total PANSS score, and to evaluate retention to assigned study treatment by percent dropout rate at the end of the study
Secondary Objectives	Objective 1: To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce positive symptoms of schizophrenia by change in Positive and General Psychopathology PANSS scores Objective 2: To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce negative symptoms of schizophrenia by change in Negative PANSS score and Motivation and Pleasure-Self Report (MAP-SR) score Objective 3: To assess safety and tolerability of PEAR-004 by adverse event monitoring and InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus) score Objective 4: To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to improve psychosocial functioning in patients with schizophrenia by change in World Health Organization Quality of Life (WHOQOL-BREF) scale Objective 5: To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce depression symptoms in patients with schizophrenia by change in Beck Depression Inventory, Second Edition (BDI-II) score Objective 6: To evaluate the magnitude of the effect of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce symptoms of schizophrenia by percentage improvement in PANSS score Objective 7: To evaluate the response to treatment by the proportion of responders

	Objective 8: To evaluate patient adherence to antipsychotic medication by change in Brief Medication Questionnaire (BMQ)
Study design	This is a randomized, sham controlled, rater-blinded, parallel group trial. Patients will be randomized 1:1 to receive PEAR-004 or a sham control. The study includes an up to 4-week screening period, a 12-week treatment period, and a 4-week follow-up period.
Population	The study will enroll approximately 102 male and female adults (18-65 years of age, inclusive) with a diagnosis of schizophrenia
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Healthy male and female subjects 18 to 65 years of age, inclusive, and in good health as determined by medical history, physical examination, and vital signs at screening • SCID-based Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia and a total PANSS score > 60 • Proficient in English at 5th grade reading level or higher, in the judgement of the investigator • Capable of using a mobile device (compatible with PEAR-004) and using common applications, in the judgement of the investigator
Key Exclusion criteria	• Major change in primary antipsychotic medication in the prior 4 weeks before screening (e.g., switching to a new agent or a major dose adjustment within two weeks of randomization) • Planning to move out of the geographic area within 3 months • Unable to use English to participate in the consent process, the interventions or assessments • Inability to comply with study procedures, due to severe medical conditions or otherwise • Meet DSM-5 diagnosis for a current episode of major depression, mania, or hypomania in the past month • Meet DSM-5 diagnosis for a current moderate or severe alcohol or cannabis use disorder in the past 2 months • Meet DSM-5 diagnosis for a current substance use disorder (other than alcohol or cannabis) in the past 2 months • Considered high risk for suicidal behavior based on ISST-Plus score at screening, in the judgement of the investigator • Previously participated in a clinical study involving PEAR-004
Study treatment	PEAR-004 Sham control
Efficacy assessments	• PANSS • BMQ • MAP-SR • WHOQOL-BREF • BDI-II
Key safety assessments	• Adverse event monitoring • Vital signs • ISST-Plus

Other assessments	Corporate Confidential Information
Data analysis	The change from baseline in total PANSS score will be analyzed using the mixed-effects model for repeated measures (MMRM), with 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. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger method will be used to adjust the estimated covariance of the mean difference and the degrees of freedom. Several other covariance structures will be tested if there are convergence issues in the primary analysis. The primary hypothesis to be tested is that mean change from baseline in PANSS is greater with PEAR-004 than with Sham at day 85 or last visit. The primary comparison will be the contrast between treatments on day 85. The significance test will be carried out using 1-sided α=0.05. In addition, two-sided 90% confidence intervals for the treatment mean differences, as well as individual treatment mean change from baseline values at each study visit will be constructed. Two sensitivity analyses (the selection model and the pattern mixture model) will be performed to assess the robustness of the primary analysis to missing data results. The LOCF approach will also be performed to aid in the interpretation of the results from the primary analysis.
Key words	Schizophrenia, prescription digital therapeutic, cognitive behavioral therapy, smartphone app

1 Introduction

1.1 Background

Schizophrenia is a common condition occurring in about 1% of the general population Saha et al 2005. It is treated with antipsychotic medications, which can help acute exacerbations of delusions or hallucinations, but do not improve the long-term course of the illness. Functional impairment is severe and disabling, and not improved by medication. Most patients are unable to work or live independently.

Cognitive-behavioral therapy (CBT) has been shown to improve symptoms of schizophrenia somewhat, both for delusions and hallucinations ("positive" symptoms) as well as for apathy and flat affect ("negative" symptoms) and functional status (engagement with employment or social interactions) Rector and Beck 2001. Access to CBT can be difficult based on cost and availability of psychotherapists. PEAR-004 is being developed as a prescription digital therapeutic (PDT), delivered via mobile devices, that delivers coping skills from evidence-based treatments such as CBT, Social Skills Training (STS), and Illness Self-Management Training (ISMT). It is intended to be used by patients who are under the care of a qualified healthcare professional and are on antipsychotic pharmacotherapy. If efficacious, it would demonstrate that 24/7 access to evidence-based coping skills, which when added to medications, may improve symptom management and functional outcomes.

PEAR-004 is intended to deliver multimodal evidence-based neurobehavioral mechanisms of action which include Cognitive Restructuring, Behavioral Activation, ISMT, and SST. Preliminary evidence has shown that patients with psychotic disorders can actively engage with software similar to PEAR-004, which suggests that PEAR-004 may improve both positive and depressive symptoms in patients with schizophrenia Ben-Zeev et al 2014; Ben-Zeev et al 2016 and serious mental illness Ben-Zeev et al 2018.

PEAR-004 is comprised of a patient-facing mobile-device application interface (via smartphone) and a clinician-facing web interface. The patient application delivers therapeutic content organized into multiple domains representing common symptoms or problem areas for patients with schizophrenia including: thoughts, voices, social functioning, medication, mood, sleep, and other coping skills for daily life. Patients are prompted to interact with PEAR-004 three times per day by automated notifications. Therapeutic content is delivered via a series of short interactions. Patients can select a therapeutic domain and choose what kind of skill they think would be most helpful. Patients then choose the specific skill and have the option of watching, reading, or listening to content about what the skill is and how they can give it a try. Patients then view tips for successful practice, and after they practice a skill are asked to provide feedback about whether the skill was helpful. Helpful skills are stored in the Toolbox to promote repeated practice and skill mastery.

PEAR-004's academic precursor is FOCUS, a software-based intervention (delivered via mobile devices) designed with input from both treatment providers and patients to optimize both usability and engagement and developed to be used in conjunction with ongoing outpatient treatment Ben-Zeev et al 2013. The feasibility, acceptability, and initial efficacy of FOCUS for improving symptoms and treatment engagement in patients with schizophrenia was established in a one month open-label trial. In this trial, overall satisfaction (91%), retention (100%), and

engagement (patients active 87.5% of trial days) were very high. Participants in this trial had significant reductions in both overall symptoms of schizophrenia and depression from baseline to end of trial Ben-Zeev et al 2014.

In a separate study Ben-Zeev et al 2016, engagement with FOCUS among patients with schizophrenia was measured during a 6-month period following psychiatric hospitalization discharge. Similar to findings from the one-month feasibility trial, patients with schizophrenia were highly engaged over the course of 6 months (active use on 82% of the weeks during which they had access to the intervention). Taken together, these preliminary findings show the promise of PEAR-004 (developed based on the academic version of FOCUS software) as a PDT for improving symptoms and treatment outcomes in patients with schizophrenia.

1.2 Purpose

The purpose of the study is to determine in patients currently being administered antipsychotic pharmacotherapy whether PEAR-004 can further reduce symptoms of schizophrenia as measured by the total score on the Positive and Negative Syndrome Scale (PANSS).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives and endpoints	
Primary Objective	
Objective	**Endpoint**
• To assess the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce symptoms of schizophrenia	• Change in total PANSS score from baseline to day 85 or last visit
• To evaluate retention to assigned study treatment	• Percent dropout rate
Secondary Objectives	
Objectives	**Endpoints**
• To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce positive symptoms of schizophrenia	• 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
• To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce negative symptoms of schizophrenia	• 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
• To assess safety and tolerability of PEAR-004	• Adverse events, serious adverse events, and adverse events leading to discontinuation throughout the study

	• 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
• To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to improve psychosocial functioning in patients with schizophrenia	• Change on the World Health Organization Quality of Life (WHOQOL-BREF) scale from baseline to day 29, day 57, and day 85 or last visit
• To evaluate the efficacy of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce depression symptoms in patients with schizophrenia	• 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
• To evaluate the magnitude of the effect of PEAR-004 as an adjunct to existing clinician-directed pharmacotherapy to reduce symptoms of schizophrenia	• Percentage change in PANSS score (within assigned group) from baseline to day 29, day 57, and day 85 or last visit
• To evaluate the response to treatment	• Proportion of responders, defined as a reduction of at least 20% at day 85 or last visit in total PANSS score relative to baseline
• To evaluate patient adherence to antipsychotic medication	• Change in antipsychotic pharmacotherapy use as measured by the Brief Medication Questionnaire (BMQ) at day 29, day 57, and day 85 or last visit

Exploratory Objectives

3 Study design

This is a randomized, sham controlled, rater-blinded, parallel group trial. Approximately 102 subjects will be randomized 1:1 in to the following groups:

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

Figure 3-1 Study Design

4 Rationale

The overall rationale for the study is to assess the first PDT in schizophrenia using evidence-based coping skills to supplement standard of care with antipsychotic medications.

4.1 Rationale for study design

- The design of this study addresses the primary objective of assessing the efficacy of PEAR-004 in subjects with schizophrenia and takes into account the novel use of a digital therapeutic to treat disease.
- Bias will be reduced by randomizing subjects to PEAR-004 or sham. Only subjects randomized to Group A will have access to the full clinical content and treatment logic of PEAR-004 and its therapeutic components.
- Raters will be blinded to randomization assignment.

4.2 Rationale for duration of treatment

No investigational medicinal product will be provided in this study; subjects will continue on their prescribed clinician-directed pharmacotherapy.

PEAR-004 is an investigational medical device, which is a prescription digital therapeutic.

The duration of treatment of 12 weeks with PEAR-004 or sham was selected based on the standard treatment duration for antipsychotic drug trials in schizophrenia to assess short-term benefit.

4.3 Rationale for choice of control

Digital therapy with PEAR-004 involves interaction with an application on a smartphone. To control for nonspecific effects of engagement with a smartphone, a sham application will be provided which does not deliver active coping skills derived from evidence-based psychosocial interventions. The sham app will include notifications 3 times per day, and when the app is opened it will display a prescription timer for the remaining duration of app availability.

4.4 Purpose and timing of 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.

4.5 Risks and benefits

There is no benefit expected for subjects participating in this study.

Appropriate eligibility criteria and stopping rules are included in this protocol.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

5 Population

Approximately 102 subjects will be enrolled in the study and randomized.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Healthy male and female subjects 18 to 65 years of age, inclusive, and in good health as determined by medical history, physical examination, and vital signs at screening
3. SCID-based DSM-5 diagnosis of schizophrenia and a total PANSS score > 60
   Kay et al 1987
4. Proficient in English at 5th grade reading level or higher, in the judgement of the investigator
5. Capable of using a mobile device (compatible with PEAR-004) and using common applications, in the judgement of the investigator

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Major change in primary antipsychotic medication in the prior 4 weeks before screening (e.g., switching to a new agent or a dose adjustment within two weeks of randomization)
2. Planning to move out of the geographic area within 3 months
3. Unable to use English to participate in the consent process, the interventions or assessments
4. Inability to comply with study procedures, due to severe medical conditions or otherwise
5. Meet DSM-5 diagnosis for a current episode of major depression, mania, or hypomania in the past month
6. Meet DSM-5 diagnosis for a current moderate or severe alcohol or cannabis use disorder in the past 2 months
7. Meet DSM-5 diagnosis for a current substance use disorder (other than alcohol or cannabis) in the past 2 months
8. Considered high risk for suicidal behavior based on ISST-Plus score at screening, or in the judgement of the investigator
9. Previously participated in a clinical study involving PEAR-004

6 Treatment

6.1 Study treatment

Details on the requirements for management of study treatment, and instructions to be followed for subject numbering, providing and utilizing study treatment are outlined in the SOM.

PEAR-004 is an investigational digital therapeutic, currently available on a mobile device (iOS and Android based). It is designed to serve as an illness self-management tool. Subjects can

access PEAR-004 as needed to receive suggestions about coping strategies to overcome difficulties in daily life.

A control sham will be available to the control group. The sham will be downloaded to the subject's phone, but will not deliver the active therapeutic content of PEAR-004. It will deliver notifications prompting the subject to open the sham app, and will then display a prescription timer for the remaining duration of app availability.

Eligible subjects will gain access to either PEAR-004 or sham according to their randomization assignment via a digital prescription access code provided to the site. Study site staff will receive training on how to download PEAR-004 or sham to the assigned subject's phone as part of site initiation activities.

6.1.1 Treatment arms/group

Subjects will be assigned on Day 1 to one of the following two treatment arms/groups in a ratio of 1:1

- PEAR-004
- Sham

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Subjects are expected to maintain their physician prescribed pharmacotherapy during the study, as specified in the exclusion criteria.

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject is enrolled into the study must be recorded on the appropriate Case Report Forms.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from raters at the site. A subject randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to treatment numbers. A separate treatment list will be produced using a validated system that automates the random assignment of treatment numbers.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a rater-blinded study. Raters will remain blinded to study treatment throughout the study.

The identity of the treatments will be concealed by limiting rater access to the randomization list, subject-specific phone, and web portal. Raters will be independent of other aspects of study conduct, and subjects will be instructed not to provide specific details about the content they are viewing on their phone to the rater.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind the rater confidential and secure until clinical database lock.

Following final database lock all roles may be considered unblinded. See the blinding/unblinding table for an overview of the blinding/unblinding plan.

Table 6-1 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	**Treatment allocation**	**Safety event (single subject unblinded)**	**Interim Analysis**
Subjects	UI	UI	UI	UI
Site staff	UI	UI	UI	UI
Raters (independent of other aspects of study conduct)	B	B	B	B
Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff	UI	UI	UI	UI
Unblinded Pharmacovigilance sponsor staff	NA	NA	NA	NA
Statistician/statistical programmer/ data analysts (e.g. biomarker)	UI	UI	UI	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	NA	NA	NA	NA
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	UI	UI	UI	UI

UI: Allowed to be unblinded on individual subject level

B: Remains blinded

NA: Not applicable to this study

6.5 Dose escalation and dose modification

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Treatment compliance here refers to subject use of PEAR-004. Data will be collected to assess frequency of subject use of PEAR-004, including whether use was prompted by a notification or subject-initiated.

Self-reported compliance with the subject's ongoing clinician-directed pharmacotherapy will additionally be assessed via the BMQ.

6.7 Treatment distribution

Each study site will be provided with access to study treatment as described under the investigational and control treatment section. See the Site Operations Manual for further details.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational treatment will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

The Assessment schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the Assessment schedule (Table 8-1) or as close to the designated day as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit the adverse event and concomitant medications should be recorded on the CRF.

Table 8-1 Assessment Schedule

Epochs	**SCREENING (Non-Treatment)**	**Treatment**				**EOS**
Visit Name	**Screening**	**Treatment**				**EOS**
Weeks		**1**	**4**	**8**	**12**	**16**
Days	**-28 to -1**	**1**	**29**	**57**	**85**	**115**
Obtain informed consent	X					
Corporate Confidential Information						
Inclusion /Exclusion criteria	S					
Relevant med history / current medical conditions	X					
Demography	X					
Physical examination	S					S*
Randomization		X				
PEAR-004/Sham distribution and data collection[1]		X	X	X	X	X
Corporate Confidential Information						
Body height	X					
Body weight	X	X[3]				X*
Vital signs (Body temp, blood pressure, pulse rate)	X	X[3]			X	X*
Concomitant meds/Therapies	X	X	X	X	X	X*
PANSS	X	X[3]	X	X	X	X*
ISST-Plus	X	X[3]	X	X	X	X*
Corporate Confidential Information						
BMQ		X[3]	X	X	X	X*
MAP-SR		X[3]	X	X	X	X*
WHOQOL-BREF		X[3]	X	X	X	X*
BDI-II		X[3]	X	X	X	X*
Corporate Confidential Information						

Epochs	**SCREENING (Non-Treatment)**	**Treatment**				**EOS**
Visit Name	**Screening**	**Treatment**				**EOS**
Weeks		**1**	**4**	**8**	**12**	**16**
Days	**-28 to -1**	**1**	**29**	**57**	**85**	**115**
Adverse Events	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X

Note: If several assessments are scheduled at the same time point, please see the SOM for guidance on recommended sequence of assessments

X = assessment to be recorded in clinical database

S = assessment to be recorded in source documentation only and will not be entered into the CRF

*These assessments are also to be conducted for subjects who discontinue study treatment

[1] Data collection from day 1 through day 85.

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[3] Assessment performed on day 1 prior to PEAR-004/Sham distribution is considered baseline.

Corporate Confidential Information

8.1 Screening

Re-screening of potential subjects is allowed if the subject fails an initial screening. Re-consenting is required.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.1.1 Eligibility screening

DSM-5 will be used to assess eligibility. SCID-based diagnosis of schizophrenia will be a paper-based assessment administered by a clinician at the screening visit.

8.1.2 Information to be collected on screening failures

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data are to be collected on all subjects. Relevant medical history/current medical condition present before signing the informed consent will be recorded. Details are outlined in the Site Operations Manual.

8.3 Efficacy

8.3.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS is a 30-item clinician-administered semi-structured interview of schizophrenia symptoms. The PANSS total score can be further broken down to subscales for positive, negative, and general symptoms.

8.3.2 Brief Medication Questionnaire (BMQ)

The BMQ is a self-report of medication usage, including what medications the patient is currently taking, how they took each medication in the past week, drug effects and bothersome features, and difficulties remembering to take their medication.

8.3.3 Motivation and Pleasure-Self Report (MAP-SR)

The MAP-SR is a 15-item self-report measure that provides a total score index of current motivation/pleasure negative symptoms.

8.3.4 World Health Organization Quality of Life (WHOQOL-BREF) Scale

The WHOQOL-BREF is a 26-item clinician-administered structured interview that assesses psychological functioning and quality of life in four primary domains: social relationships, psychological, physical, and environment.

8.3.5 Beck Depression Inventory, Second Edition (BDI-II)

The BDI-II is a 21-item self-report measure that provides a total score index of current depression symptom severity.

8.3.6 Appropriateness of efficacy assessments

These assessments are considered standard for schizophrenia, and for the specific outcomes being measured, such as depression and quality of life.

8.4 Safety

Safety assessments are specified below with the Assessment schedule (Table 8-1) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical examination	A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital sign	Vital signs include BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

The methods for each assessment and data recording details are specified in the SOM.

8.4.1 InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus)

Prospective suicidality will be assessed by the ISST-Plus, a clinician-administered semi-structured interview. The ISST-Plus is an updated version of the scale used in the InterSePT trial Ayer et al 2008, which was a Novartis-sponsored Phase III trial of treatment of suicidality with clozapine. The ISST-Plus is specifically designed for use in schizophrenia Sheehan et al 2014, and meets Health Authority criteria for suicidality assessments CDER 2012.

8.4.2 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

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8.5.3 Other Assessments

No additional tests will be performed on subjects entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

- Study treatment must be discontinued if the subject withdraws consent.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the Assessment schedule (Table 8-1), especially the day 85 and EOS (day 115) visits. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

In order to better adhere to the intent-to-treat principle, subjects will be encouraged to continue in the trial even if they discontinue treatment (often referred to as "retrieved dropout").

9.1.4 Study stopping rules

Study procedures will be stopped if the Sponsor considers that the number and/or severity of AEs or abnormal safety monitoring tests justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study digital therapeutic development

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion (EOS) visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subjects and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
2. its relationship to the study treatment or conduct. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial treatment, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding study treatment
6. its outcome i.e., its recovery status or whether it was fatal

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening
    - Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that

hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

10.1.3.1 Screen Failures

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period (following the last administration of study treatment) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.2 Additional Safety Monitoring

10.2.1 Prospective suicidality assessment

The ISST-Plus is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The ISST-Plus must be administered at each visit, including unplanned visits.

The ISST-Plus, which uses a semi-structured interview to probe subject responses, will be administered by an individual who has received training and certification in its administration.

If, at any time after screening and/or baseline, there is a notable clinical worsening in suicidal ideation or behavior, the subject should be evaluated by a mental health care professional for further assessment and/or treatment, if not already under active clinical care. The decision on whether the study treatment should be discontinued is to be taken by the investigator in collaboration with the treating mental health professionals.

In addition, all life-threatening events must be reported as SAEs. All events of “Non-Suicidal Self-Injurious Behavior” should be reported as AEs and assigned the appropriate severity grade.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, and allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the subject will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/ delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being distributed and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 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 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 unblinding.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment group for the FAS and the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 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.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

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.

12.4.2 Statistical model, hypothesis, and method of analysis

The change from baseline in total PANSS score will be analyzed using the mixed-effects model for repeated measures (MMRM) Mallinckrodt et al 2001, including 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. 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.

12.4.3 Handling of missing values/censoring/discontinuations

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.

12.4.4 Sensitivity and Supportive analyses

12.4.4.1 Sensitivity analyses

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

12.4.4.2 Supportive analyses

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.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoint(s)

The secondary efficacy endpoints listed below will be analyzed separately using an MMRM analysis. The change from baseline to each post-baseline visit will be the dependent variable. 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). The analysis strategy will be the same as for the primary outcome (Section 12.4.2). 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, as described in Section 12.4.2. Estimates of mean percentage change from baseline to each study visit with (90% CIs) will be obtained for each treatment group.

12.5.2 Safety endpoints

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).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on AEs will be displayed by treatment group and subject.

The number (and percentage) of subjects with AEs will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related AEs, death, SAEs, and other significant AEs leading to discontinuation.

A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities as well as clinically notable values will be flagged. Summary statistics will be provided by treatment and visit/time.

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.

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Approximately 102 subjects will be randomized in a 1:1 ratio to one of two treatment groups: Sham and PEAR-004. This sample size will provide 80% power to detect a statistically significant difference between the two groups at a 1-sided alpha=0.05 when the true mean difference is 8 points assuming SD =16 (common to the two groups). This difference is equivalent to a standardized effect size of 0.5, which is considered a moderate effect size, and is consistent with prior randomized controlled trials (RCTs) of cognitive behavioral therapy (CBT) in schizophrenia.

Table 12-1 shows the values of power for the true mean treatment difference in the range from -4 to -10.

Table 12-1 Sensitivity of power to changes in assumptions for a design with N=102 evaluable subjects

Allocation ratio	SD (common to 2 arms)	True mean difference (Δ)	True effect size (Δ/SD)	α (1-sided)	Power
1:1	16	-4	-0.25	0.05	35%
1:1	16	-6	-0.375	0.05	59%
1:1	16	-8	-0.5	0.05	81%
1:1	16	-10	-0.625	0.05	93%

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol,

written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meeting or site initiation visit.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational treatments under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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