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Synoptic Clinical Study Report

A Pilot-Study in Rwandan Health Care Settings to Examine the Feasibility of a Large Pragmatic Clinical Study to Assess the Value of Paliperidone Palmitate in Rwanda

Protocol R092670PSY4001; Phase 4

R092670 Paliperidone palmitate

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Protocol No.: R092670PSY4001

Title of Study: A Pilot-Study in Rwandan Health Care Settings to Examine the Feasibility of a Large Pragmatic Clinical Study to Assess the Value of Paliperidone Palmitate in Rwanda

Name of Active Ingredient: R092670 Paliperidone palmitate

NCT No.: NCT03713658

Clinical Registry No.: CR108551

Coordinating Investigator: Bizoza Rutakayile, MD - CARAES Ndera Neuro-Psychiatric Hospital, PPD, Rwanda

Study Center(s): Rwanda (3 sites)

Publication (Reference): None

Study Period: 18 October 2018 to 02 December 2019

Phase of Development: 4

OBJECTIVES:

The objectives of this study were:

Primary Objective

The primary objective of this study was to evaluate the feasibility of conducting a study of oral risperidone followed by PP1M and PP3M in Rwandan healthcare facilities with mental healthcare capabilities. Success in this study was based on completing routine clinical study procedures, reliable delivery and administration of risperidone/PP1M/PP3M to participants throughout the study, adequate satisfaction with all study procedures, and acceptable burden on the participants, caregiver participants, and clinicians.

Secondary Objective

The secondary objective of this study was to evaluate safety and efficacy of risperidone, PP1M, and PP3M in study participants in the Rwandan healthcare system and to evaluate feasibility and value of Screener for Mental Illness with Lay Evidence (SMILE).

Endpoints

The endpoints of this study were the successful completion of the following:

- Study procedures for participants
- Adequate record keeping at each site where data was collected
- Training of clinical staff for administering risperidone/ long acting formulation of paliperidone palmitate (R092670) for once monthly intramuscular injection (PP1M)/ long-acting formulation of paliperidone palmitate (R092670) for intramuscular administration every 3 months (PP3M)
- Delivery of risperidone/PP1M/PP3M for each participant and the site where study was conducted for the duration of the study
- Administration of risperidone/PP1M/PP3M to participants for the duration of the study

- All documentation required for the study
- All case report forms (CRFs) at each study visit
- All assessments used in the study:
  - Mini International Neuropsychiatric Interview (MINI - MINI Screen and Module K) diagnostic for Schizophrenia by qualified personnel
  - Intent-to-Attend (ITA) Plus
  - Client Service Receipt Inventory (CSRI)
  - Cost Assessment Questionnaire (CAQ)
  - Sheehan Disability Scale (SDS)
  - Study safety documentation (J&J Adverse Events, Concomitant Medications, Past Medical History, Demographics Scales)
  - Study efficacy documentation:
  - SMILE – Psychosis
  - Clinical Global Impressions – Severity of Schizophrenia (CGI-SS)
  - Patient Satisfaction and Burden Rating
  - World Health Organization Quality of Life Scale Brief Version (WHO QoL-BREF)
  - Clinician Satisfaction Rating
  - Qualitative Interview and Scale Cognitive Debriefing for patient
  - Qualitative Interview and Scale Cognitive Debriefing for key clinical staff.

Refer to Section 8 of the study protocol (Appendix 1) for evaluations related to endpoints.

Note: Due to insufficient principal investigator (PI) availability and study oversight, lack of compliance with good clinical practices, and the determination that increased sponsor operational efforts would not ameliorate the observed compliance concerns, the sponsor decided to close the pilot study early. Based on the data collected and all accounts from investigators and site staff, the ongoing participants responded and tolerated paliperidone palmitate well. The sponsor determined it was in the best interest of the participants to continue to receive paliperidone palmitate through a post-trial access program with PP3M upon study closure. The R092670PSY4001 study met its objective in confirming that it was not possible to move forward with the open-label pragmatic study immediately following this feasibility study as originally planned unless a significant effort was made to improve research capacity.

METHODS:

Overview of Study Design

This was an open-label, uncontrolled, multicenter, interventional study conducted at multiple sites in Rwanda that examined the feasibility of administering paliperidone palmitate in participants with schizophrenia. The study included the following phases: 1) screening; 2) run-in of risperidone for tolerability testing (3 mg); 3) lead-in treatment with PP1M (50-, 75-, 100-, or 150-mg eq. per product label); and 4) maintenance treatment with PP3M (175- to 525-mg eq. per product label). Screening for participants was performed for up to 4 weeks to confirm eligibility for participation in the study.

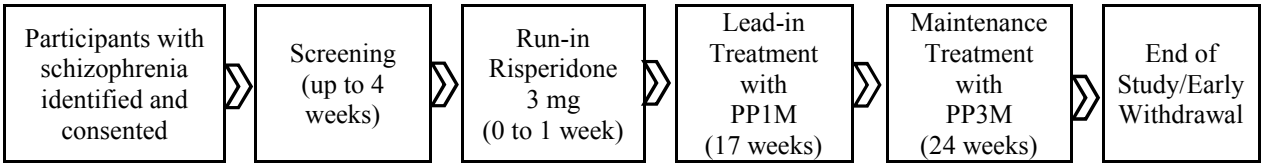
Before participant enrollment, each site was assessed for capability to perform protocol assessments and ability to dispense and administer medications used in this study in a reliable and medically appropriate

manner. This review was performed by taking a mock participant through all aspects of the study that were to be performed on Day 1 of PP1M treatment, including the procedures for study medication administration (injection), thereby simulating protocol and clinical requirements for successful completion of the study at each site.

A participant was considered to have completed the study when he or she had completed assessments at Week 45 of Phase 2 of the PP3M treatment phase. For participants who withdrew early, the assessments scheduled to be collected at end of study visit were to be collected at their last study visit. The end of study was considered as the last scheduled study assessment for the last participant in the study as described in the study protocol (Appendix 1).

A diagrammatic representation of the study design is presented in Figure 1.

Figure 1: Schematic Overview of the Study



Key: PP1M= long acting formulation of paliperidone palmitate (R092670) for once monthly intramuscular injection; PP3M= long acting formulation of paliperidone palmitate (R092670) for intramuscular administration every 3 months

The schedule for the various study procedures and evaluations are described in detail in the study protocol (Appendix 1).

Number of Subjects (planned and analyzed):

Planned: A target of approximately 30 participants were planned for this study.

Analyzed: A total of 33 participants were enrolled and received paliperidone palmitate (PP1M/PP3M).

Diagnosis and Main Criteria for Inclusion:

The target population consisted of male participants and female participants of non-childbearing potential aged >18 to <70 years at screening and with a confirmed diagnosis of schizophrenia by MINI-Screen and MINI Module K that required treatment initiation or a change in treatment to better address safety or efficacy limitations of current treatment.

Inclusion Criteria

Participants enrolled in this study were required to meet the following additional key acceptance criteria:

1. speak Kinyarwanda, French, or English
2. eligible for treatment in the Rwandan mental healthcare system
3. at least moderately ill as measured by the CGI-SS scale for schizophrenia, or experiencing poorly tolerated side effects from their current medications, or having difficulty with adequate adherence to treatment, per the investigator's judgement
4. has a primary caregiver who is willing to participate in this study (caregiver should be knowledgeable about the participant's condition and is expected to be with the participant for >24 hours each week for the duration of the study)
5. able to give consent to participate in a clinical study that includes treatment with risperidone and long-acting injectable formulations of paliperidone palmitate. Participants must be willing to receive

injections. The participant and the caregiver participant must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study

6. intends to attend all follow-up appointments with their caregiver at one of the study sites (or at a designated secondary district or provincial hospital participating in this study)
7. must be willing and able to provide responses for all self-administered questionnaires.

Exclusion Criteria

Potential participants were excluded from participating in the study if they met any of the following criteria:

1. has a physical, mental, or legal incapacity that prevents a valid consent or capacity to complete about 12 months of treatment with antipsychotic medication and compliance with this study protocol (Appendix 1)
2. history of organic brain syndromes, comorbid psychiatric and/or physical illnesses, or significant comorbid substance abuse that is likely to interfere with understanding of or compliance with study requirements
3. known allergies, hypersensitivity, or intolerance to risperidone or paliperidone palmitate or their excipients (refer to Investigator's Brochure).[1,2]
4. poor prior response to risperidone
5. received an investigational medication (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study medication, or is currently enrolled in an investigational study
6. pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study medication
7. any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Participant Withdrawal

A participant was not automatically withdrawn from the study if he/she discontinued study medication before the end of the treatment phase. A participant was to be withdrawn from the study for any of the following reasons: 1) lost to follow-up, 2) withdrawal of consent, 3) death, and 4) if the participant was not clinically stabilized even after 3 additional cycles of PP1M (last 2 consecutive doses are same) after the Visit 8 in the lead-in treatment phase.

When a participant withdrew before completing the study, the reason for withdrawal was to be documented in the electronic CRF (eCRF) and source document. Study medication assigned to the withdrawn participant was not assigned to another participant. When a participant discontinued study medication and withdrew from the study before the end of treatment phase, end-of-study visit assessments were to be obtained if the participant was willing to complete that visit. When the reason for withdrawal from the study was withdrawal on consent, no additional assessments were allowed.

Re-entry was allowed into this study. Participants records were not to be closed until their last expected day of study participation.

Test Product, Dose and Mode of Administration, Batch No.:

During the run-in phase, after completing screening, participants started treatment with oral risperidone tablets (3 mg daily) to establish participant's tolerability based on investigator judgement.

Participants completing the run-in phase with oral risperidone who demonstrated tolerability were started on PP1M. The first dose of PP1M was 150 mg eq. given in the deltoid muscle at Day 1 of the treatment phase. The second dose of PP1M was 100 mg eq. given in the deltoid muscle at Day 8 (±4 days). Subsequent doses of PP1M beginning on Day 36 were given every 28 (±7) days in either the deltoid or gluteal muscle. The investigator selected from 50, 75, 100, and 150 mg eq., according to the participants' clinical safety, tolerability, and efficacy requirements. Participants continued to return every 4 weeks for injections and for study evaluations.

When a stable dose was identified for PP1M (last 2 doses of PP1M administered at consecutive visits were the same), participants started PP3M treatment at the next visit (after 28±7 days). The initial PP3M dose was a 3.5-fold multiple of the final PP1M dose administered at last visit. Investigators were permitted to flexibly adjust the dose of PP3M as clinically necessary with the dose options for PP3M being 175, 263, 350, or 525 mg eq. Injections of PP3M were administered in either the deltoid muscle or the upper-outer portion of the gluteal muscle.

The study treatment lot numbers and expiration information are presented in Table 1.

Table 1: Study Treatment Lot Numbers and Expiration Information

Study Drug Name	Packaged Lot Number	Bulk Lot Number(s)	Expiry Date
Oral risperidone 3 mg	4376943	J69387, J70101	31-Aug-19
Paliperidone palmitate 50 mg eq.	4376847	IDB4V	1-Apr-20
Paliperidone palmitate 75 mg eq.	4376848	ICB70	1-Mar-20
Paliperidone palmitate 100 mg eq.	4376849	IBB6B	1-Feb-20
Paliperidone palmitate 100 mg eq.	4378612	IBB6B	1-Feb-20
Paliperidone palmitate 150 mg eq.	4376977	IDB55	1-Apr-20
Paliperidone palmitate 175 mg eq.	4377263	IDB2P00	1-Apr-20
Paliperidone palmitate 263 mg eq.	4377265	ICB0000	1-Mar-20
Paliperidone palmitate 350 mg eq.	4377266	ICB1C00	1-Mar-20
Paliperidone palmitate 525 mg eq.	4377264	IDB2R00	1-Apr-20

Duration of Treatment:

The planned study duration was approximately 46 weeks for each participant: 1) screening (up to 4 weeks), 2) run-in of risperidone for tolerability testing (0 to 1 week); 3) lead-in treatment with PP1M (approximately 17 weeks), and 4) maintenance treatment with PP3M (up to 24 weeks).

Criteria for Evaluation:

Efficacy Assessments

MINI

The MINI-Plus is a structured and standardized diagnostic interview used to determine the most common psychiatric disorders according to axis I of Diagnostic and Statistical Manual of Mental Disorders-IV-TR and the International Classification of Diseases and Related Health Problems.

After a participant was determined to be qualified via the MINI Screen tool (a subset of the complete MINI used as a tool for preselection of participants), Module K of the MINI (a brief, structured diagnostic interview) was to be applied in order to confirm the diagnosis of schizophrenia and to determine if other psychiatric conditions were present.

Screener for Mental Illness With Lay Evidence – Psychosis

The Psychosis module of the SMILE was used to assess the clinical symptoms of schizophrenia. Both the participant and caregiver participant completed the 15-item Likert scale with a 5-point range (never to all the time). The objective in this study was to assess and evaluate both the benefit of the SMILE to the participant in a Rwandan healthcare setting and that the scale was sensitive to change.

Clinical Global Impression - Severity of Schizophrenia

The CGI-SS was used to provide a clinical measure of the severity of schizophrenia experienced at the time of the visit. The assessment is a single-item Likert scale with a 7-point range (none to extreme symptoms).[3] It was completed after the site provider had reviewed the SMILE and other available information from the participant, the caregiver participant, and any other available persons regarding symptomatic information on the participant.

Safety and Other Assessments

Safety and other assessments were based on reported adverse events (AEs), clinical laboratory tests, concomitant medications, past medical history, demographics, physical examinations, vital sign measurements, electrocardiograms (ECGs), and suicidal risk monitoring and behavior risk monitoring.

Suicidal Risk Monitoring and Behavior Risk Monitoring

Participants being treated with risperidone and paliperidone palmitate were monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration was to be given to discontinuation of risperidone and paliperidone palmitate in participants who experienced signs of suicidal ideation or behavior.

Participants' suicidal ideation and behavior during the study were to be tracked and evaluated using the screening section of the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. It can also be used during treatment to monitor for clinical worsening.

Satisfaction Assessments

The following satisfaction assessments were performed to access the satisfaction level of participants, caregivers, and health care providers.

WHO QoL-BREF

A shortened version of the WHO QoL-BREF (25-item Likert scale with a 4-point range for each response [1 to 5]) was used to assess participant and caregiver burden and satisfaction with the study (especially any change before and after the introduction of long-acting injectable [LAI]).

Clinician Satisfaction Rating

The Clinician Satisfaction Rating is a 4-item scale. Two items used a Likert scale with a 6-point range (0/definitively not to 6/definitely) and 2 items were multiple-choice. This scale was used to assess the acceptability and/or burden for the provider associated with the study including treatment with LAIs.

Qualitative Interview and Cognitive Debriefing

A semi-structured interview and cognitive debriefing of participants were conducted at the end of the study for each participant. The interview covered all aspects of the study and was used to find solutions for any problems that were discovered.

Outcome Assessments

Intent-to-Attend Plus

The ITA Plus scale (single Likert scale question with a range of 0 to 6 [definitely not to definitely]) was used to estimate the likelihood of completing the study or attending the next visit. If the participant provided a subthreshold likelihood response, a follow-up open-ended question was posed that provided qualitative feedback on why completion/attendance did not occur.

Sheehan Disability Scale

The SDS (5-item scale) was used to assess the functioning of participants with schizophrenia.

End-of-Study/Early Withdrawal Evaluation Form

The end-of-study/early withdrawal evaluation form was to be used to document and assess the reasons for participant withdrawal from the study.

Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, were collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters were excluded. The collected data could be used for exploratory economic analyses.

The CSRI and CAQ were used to assess the direct and indirect costs, respectively, of schizophrenia care for participants, caregivers, and health care providers.

Data Quality Assurance:

The study was monitored according to the sponsor's current Standard Operating Procedure (SOP) for the Monitoring of Clinical Trials. Steps taken to ensure the accuracy and reliability of the clinical study data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated study-site personnel prior to study start, and periodic monitoring visits by the sponsor or their delegate. The study-specific monitoring guidelines are stored in the trial master file (TMF). The sponsor could conduct investigator site audits.

During the course of this study, several activities were implemented to ensure proper operational study oversight (documented in the TMF). These activities were focused on identification and resolution of operational and quality issues to ensure data integrity, protocol compliance, and safety of the study participants.

Written instructions were provided for the collection of source documentation. Source documentation was reviewed for accuracy and completeness by the sponsor during on-site monitoring visits, except for source data directly transmitted from the selected laboratory into the sponsor's database. Internal data reviews were conducted by various functions throughout the study and at the time of database lock. Discrepancies were resolved with the investigator or designees, as appropriate.

Statistical Methods:

Sample Size Determination

The proposed sample size was based on a convenience sample to assess the feasibility of being able to carry out future clinical study in this environment. A sample size of 30 participants was deemed appropriate to allow for the estimate of the parameters with an adequate degree of precision and expected to provide enough information to proceed to conduct a large pragmatic clinical study.

Planned Analyses

Feasibility Analyses

Feasibility for moving forward beyond this study was primarily established following qualitative review of incoming data from this study. The following 5 major domains of feasibility were examined:

1. Drug supply: Whether PP1M and PP3M were reliably supplied to Rwandan sites of care for uninterrupted long-term use in patients?
2. Patients: Whether appropriate schizophrenic patients were identified in the Rwandan mental health system who accepted regular injections with an injectable antipsychotic medication?
3. Training: What procedures and materials were necessary to train mental health care professionals in Rwanda on how to safely and effectively use PP1M and PP3M?
4. Data collection: Whether data was reliably collected that demonstrated the safety and effectiveness of PP1M and PP3M when used in a real-world Rwandan mental health setting?
5. Scales: Were the scales proposed for this study understood by those completing them? Was the burden acceptable? Did they support the outcomes needed?

Qualitative analysis for each of these domains included evaluation of whether a problem existed in that domain, the severity of any problem identified, its potential impact on the conduct of the follow-on pragmatic clinical study and the ability to correct it so that the pragmatic study was successful.

Efficacy Analyses

All efficacy analyses were planned to be carried out using the evaluable population that was defined as all enrolled participants who received at least one dose of PP1M or PP3M. The efficacy endpoints included the changes from baseline to end of study for the following scales: the CGI-SS and SMILE-Psychosis. The efficacy analyses were to include descriptive statistics reporting means and standard deviations at baseline and endpoint as well as changes from baseline with the 90% confidence interval.

Safety Analyses

Safety and tolerability assessments were to be summarized using descriptive statistics.

Treatment-emergent adverse events (TEAEs) were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1. Summaries, listings, datasets, or participant narratives are provided.

Laboratory data were to be summarized by type of laboratory test. Descriptive statistics were to be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results were to be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Physical examination findings, including weight, were to be summarized at each scheduled time point. Descriptive statistics were to be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

Descriptive statistics of temperature, heart rate, and blood pressure (systolic and diastolic) values and changes from baseline were to be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits were to be reported.

The ECG variables for analysis were to include heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using some or all of the following correction methods: QT corrected according to Bazett's formula, QT corrected according to Fridericia's formula. Descriptive statistics of

QTc intervals and changes from baseline were to be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds and the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds were to be summarized.

Suicide-related thoughts and behaviors based on the C-SSRS scale were to be summarized in incidence and shift tables.

Medical Resource Utilization and Health Economics

Medical resource utilization and health economics were to be descriptively summarized.

Other Analyses

Descriptive statistics were to be summarized for the other endpoints. For continuous variables, means and standard deviations at baseline and endpoint were to be presented. In addition, mean changes from baseline with their corresponding 90% confidence intervals were to be presented. For categorical variables, frequency distributions were to be presented at all time points. Summary measures of all scales that were successfully completed were also to be presented.

Interim Analysis

No interim analysis was planned for this study.

Changes in Planned Analyses

Due to nature of this study (a feasibility study) and the early closure, the scope of analyses and clinical study report were limited. The sponsor decided that only raw data listings would be provided for most data domains and a few data summaries would be provided for data domains including demographics, disposition, number of injections, and basic AE summaries.

It was also decided that no statistical analysis plan would be needed.

RESULTS:

Due to insufficient PI availability and study oversight, lack of compliance with good clinical practices (related to clinical trial processes and documentation, not as a result of a safety signal or concern), and the determination that increased sponsor operational efforts would not ameliorate the observed compliance concerns, the sponsor decided on 16 July 2019 to close the study. The sponsor determined it was in the best interest of the participants to continue to receive paliperidone palmitate through a post-trial access program upon study closure.

STUDY POPULATION:

Participant Disposition and Study Completion/Withdrawal Information

A total of 33 participants were enrolled in this study and received paliperidone palmitate (PP1M/PP3M). Of these, only 2 participants completed the study and 31 participants were discontinued prematurely from the study. Among the discontinued participants, 29 (87.9%) participants were discontinued due to sponsor's decision (Table 2).

Table 2: Completion/Withdrawal Information During the Study; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Analysis set: All Evaluable	33
Completed	2 (6.1%)

Table 2: Completion/Withdrawal Information During the Study; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Terminated study participation prematurely	31 (93.9%)
Reason for termination	
Study terminated by sponsor	29 (87.9%)
Disease relapse	1 (3.0%)
Withdrawal by subject	1 (3.0%)

Key: OL = open-label, PP1M = long acting formulation of paliperidone palmitate (R092670) for once monthly intramuscular injection, PP3M = long acting formulation of paliperidone palmitate (R092670) for intramuscular administration every 3 months
Percentage calculated with the number of subjects in each group as the denominator.

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A listing of study completion or withdrawal information of each participant is presented in Appendix 13 (LSIDS01).

Demographics and Baseline Characteristics

A summary of demographics and baseline characteristics for all participants is presented in Table 3.

Of the 33 participants enrolled in this study, 17 (51.5%) participants were male and 16 (48.5%) participants were female. All participants belonged to the Black or African American race with a mean (SD) age of 42.0 (12.12) years and mean (SD) body mass index and baseline weight of 24.5 (5.61) kg/m^2 and 66.7 (14.25) kg, respectively.

Table 3: Demographic and Baseline (OL) Characteristics; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Analysis set: All Evaluable	33
Age, years	
N	33
Mean (SD)	42.0 (12.12)
Median	42.0
Range	(22; 66)
18-25 years	3 (9.1%)
26-50 years	21 (63.6%)
51-65 years	8 (24.2%)
>65 years	1 (3.0%)
Sex	
N	33
Female	16 (48.5%)
Male	17 (51.5%)
Race	
N	33
Black or African American	33 (100.0%)
Weight, kg	
N	33
Mean (SD)	66.7 (14.25)
Median	64.0
Range	(51; 113)
Height, cm	
N	33
Mean (SD)	165.2 (7.99)
Median	166.0

Table 3: Demographic and Baseline (OL) Characteristics; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Range	(148; 184)
Body mass index, kg/m^2	
N	33
Mean (SD)	24.5 (5.61)
Median	22.0
Range	(18; 46)
Underweight <18.5	1 (3.0%)
Normal 18.5-<25	21 (63.6%)
Overweight 25-<30	5 (15.2%)
Obese ≥30	6 (18.2%)
Waist Circumference, cm	
N	29
Mean (SD)	84.38 (17.815)
Median	83.80
Range	(29.0; 119.4)

Key: OL = open-label, PP1M = long acting formulation of paliperidone palmitate (R092670) for once monthly intramuscular injection, PP3M = long acting formulation of paliperidone palmitate (R092670) for intramuscular administration every 3 months, SD = standard deviation

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A listing of demographics for each participant is presented in Appendix 16 (LSIDEM01).

A listing of prior and concomitant medications is presented in Appendix 16 (LSICM01). Haloperidol and Largactil® (chlorpromazine) were the most commonly used prior medications.

Protocol Deviations

A listing of deviations reported during the study is presented in Appendix 14 (LSIDEV01). Eleven protocol deviations were reported, of which 7 protocol deviations were coded as 'other', 3 protocol deviations were coded as 'entered but did not satisfy criteria', and 1 protocol deviation was coded as 'received wrong treatment or incorrect dose'.

Extent of Exposure

Table 4 presents the frequency distribution of participants who received study treatment during the study. All enrolled participants received PP1M, and most of them (32 participants) received at least 1 injection of PP3M. The participant who did not receive the dose of PP3M discontinued the study prior to the scheduled dosing of PP3M (Appendix 16 [LSIEX01] and Appendix 13 [LSIDS01]); a protocol deviation coded as 'received wrong treatment or incorrect dose' was reported against him and the participant was withdrawn due to a relapse.

Table 4: Frequency Distribution of Total Number of Subjects Receiving Study Medication During the Study; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Analysis set: Evaluable	33
Total number of PP1M received	33
4	1 (3.0%)
6	29 (87.9%)
7	3 (9.1%)

Table 4: Frequency Distribution of Total Number of Subjects Receiving Study Medication During the Study; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Total number of PP3M received	32
1	30 (93.8%)
2	2 (6.3%)

Key: OL = open-label, PP1M = long acting formulation of paliperidone palmitate (R092670) for once monthly intramuscular injection, PP3M = long acting formulation of paliperidone palmitate (R092670) for intramuscular administration every 3 months

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A listing of study treatment provided for each participant is presented in Appendix 16 (LSIEX01).

EFFICACY RESULTS:

Due to the early termination of the study, efficacy analyses were not performed as planned. Listings of MINI scores at screening visits (Appendix 18 [LEFMN01]), SMILE data by caregiver (Appendix 18 [LEFSMC01]) and by participant (Appendix 18 [LEFSMP01]), and CGI data (Appendix 18 [LEFCGI01]) are presented in Appendix 18.

FEASIBILITY RESULTS:

As documented in the study monitoring visit reports according to the current standard operating procedures, following observations were noted.

1. Drug supply: During the study the investigational product PP1M and PP3M were reliably supplied to Rwandan sites of care for uninterrupted long-term use in patients. However, its long-term use was not achieved due to the early study closure.
2. Patients: Investigators were able to identify appropriate patients with schizophrenia in the Rwandan mental health system who accepted regular injections with an injectable antipsychotic medication. They were able to exceed the enrollment target of 30 participants.
3. Training: Mental health care professionals in Rwanda were successfully trained on safe and effective use of PP1M and PP3M. There was 1 case of double dose of PP1M that didn't result in a safety concern. However, there were no other serious issues recorded with regards to appropriate dosing and administration of PP1M and PP3M.
4. Data collection: There were serious issues with reliable data collection that required additional efforts from the study management team to ensure appropriate data integrity and adequate record keeping. For future studies, efforts should be made to improve ability of the study investigators to reliably collect data.
5. Scales: The scales used in this study were considered as poorly translated into Kinyarwanda and the study participants and staff had difficulty understanding them. Some of the scales, specifically the Health Economic scales need to be adjusted to the Rwandan context. Although the outcomes were perceived as useful and needed for appropriate participant evaluation, they were deemed as burdensome.

SAFETY RESULTS:

Adverse Events

Table 5 presents a summary of TEAEs classified by MedDRA system of class and preferred term. The event of overdose mentioned under Injury, poisoning, and procedural complications in this table refers to dosing error.

A total of 12 (36.4%) participants who received PP1M/PP3M reported at least 1 TEAE. The following disorders were reported in more than 2 participants: Gastrointestinal disorders (4 [12.1%] participants); General Disorders and Administration Site Conditions (3 [9.1%] participants); Infections and Infestations, Metabolism and Nutrition Disorders, Nervous System Disorders, and Psychiatric Disorders (2 [6.1%] participants each). Hyperglycemia was the only TEAE reported by more than 1 participant (2 [6.1%] participants).

Table 5: Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term During the Study; All Evaluable Analysis Set (Study R092670PSY4001)

	OL PP1M/PP3M
Analysis set: All Evaluable	33
Subjects with 1 or more TEAEs	12 (36.4%)
System organ class Preferred term	
Gastrointestinal disorders	4 (12.1%)
Abdominal pain	1 (3.0%)
Constipation	1 (3.0%)
Nausea	1 (3.0%)
Salivary hypersecretion	1 (3.0%)
General disorders and administration site conditions	3 (9.1%)
Fatigue	1 (3.0%)
Injection site pain	1 (3.0%)
Thirst	1 (3.0%)
Infections and infestations	2 (6.1%)
Bronchitis	1 (3.0%)
Malaria	1 (3.0%)
Metabolism and nutrition disorders	2 (6.1%)
Hyperglycaemia	2 (6.1%)
Nervous system disorders	2 (6.1%)
Dizziness postural	1 (3.0%)
Dyskinesia	1 (3.0%)
Psychiatric disorders	2 (6.1%)
Delusion	1 (3.0%)
Hallucination	1 (3.0%)
Insomnia	1 (3.0%)
Restlessness	1 (3.0%)
Injury, poisoning and procedural complications	1 (3.0%)
Overdose	1 (3.0%)
Investigations	1 (3.0%)
Electrocardiogram T wave amplitude decreased	1 (3.0%)
Musculoskeletal and connective tissue disorders	1 (3.0%)
Nuchal rigidity	1 (3.0%)
Respiratory, thoracic and mediastinal disorders	1 (3.0%)
Epistaxis	1 (3.0%)

Key: AE = adverse event, PP1M = long acting formulation of paliperidone palmitate (R092670) for once monthly intramuscular injection, PP3M = long acting formulation of paliperidone palmitate (R092670) for intramuscular administration every 3 months
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using the MedDRA Version 21.1.

A listing of TEAEs is presented in Appendix 19 (LSFAE01). Treatment-emergent adverse events are AEs with onset during the medication phase or that were a consequence of a pre-existing condition that had worsened since baseline.

A serious adverse event (SAE) of hyperglycemia was reported in 1 participant during the maintenance phase of the study. The participant was hospitalized, and the study treatment was discontinued due to this SAE. The event was reported as resolving and assessed by the investigator as related to the study treatment. A narrative for this SAE is available in Attachment Subject_Narrative. A listing of treatment-emergent SAEs reported during the study is presented in Appendix 19 (LSFAE02). A listing of TEAE which resulted in study treatment discontinuation is presented in Appendix 19 (LSFAE03-A).

Other Assessments

Vital Signs

A listing of vital sign data collected during the study is presented in Appendix 19 (LSFVIT01). There were no clinically significant abnormal results observed in vital signs.

Electrocardiograms

A listing of ECG data collected during the study is presented in Appendix 19 (LSFECG01). A nonserious AE of electrocardiogram T wave amplitude decreased (reported term: abnormal ECG [T waves flat]) was reported (on Day 274) in the maintenance phase of the study. This AE was assessed by the investigator as probably related to the study treatment. The outcome of this event was unknown (Appendix 19 [LSFECG01 and LSFAE01]).

Clinical Safety Laboratory Assessment Results

A listing of laboratory results on serum chemistry, hematology, and urinalysis collected during the study is presented in Appendix 20 (LSFLAB01). Local laboratory centers were used for this study. The normal range flags based on the criteria per laboratory center were included in the database.

A 48-year-old male reported a nonserious AE of hyperglycemia on Day 262. A high glucose level of 13.17 mmol/L (reference range: 4.11 to 5.89 mmol/L) was reported on Day 274 (early withdrawal visit). This AE was assessed by the investigator as probably related to the study treatment. The outcome of this event was unknown (Appendix 20 [LSFLAB01] and Appendix 19 [LSFAE01]).

A 66-year-old male reported a nonserious AE of hyperglycemia on Day 153 with a high glucose level of 32.67 mmol/L (reference range: 4.11 to 5.89 mmol/L). An SAE of hyperglycemia was reported by this participant on Day 163 (maintenance phase) with a high glucose level of 27.04 mmol/L. The AE and SAE were assessed by the investigator as probably related and related, respectively, to the study treatment. The outcome of these events were reported as resolving (Appendix 20 [LSFLAB01] and Appendix 19 [LSFAE01]).

Suicidal Risk Monitoring and Behavior Risk Monitoring

A listing of C-SSRS data collected during the study is presented in Appendix 19 (LSFCSSR01).

Satisfaction Assessment Results

A listing of clinical satisfaction rating data collected during the study is presented in Appendix 19 (LSFCSR01). Most of the participants were either satisfied or very satisfied with the study treatment.

A listing of WHOQoL-BREF data collected during the study is presented in Appendix 19 (LSFQOL01).

Outcome Assessments Results

A listing of ITA Plus data collected during the study is presented in Appendix 19 (LSFITA01). For most of the participants, a numerical score of 6 was noted. These participants definitely intended to attend the next scheduled visit. Only 1 participant had a score of 1 in the maintenance phase (early withdrawal visit). This participant was very unlikely to attend the next scheduled visit.

A listing of SDS collected during the study is presented in Appendix 19 (LSFSDS01). The functioning of most participants as assessed by SDS was either mildly or not at all affected.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS RESULTS:

A listing of CSRI and CAQ collected during the study is presented in Appendix 19 (LSFCSCA01).

Study Limitations:

The data collected in this study was not intended to be used for quantitative analysis or publication purposes. It should permit the sponsor to make better decisions about the strategic issues in planning of future projects.

CONCLUSIONS:

Rwanda was selected for participation in this feasibility study as party of a larger Global Public Health strategy to promote the development of sustainable healthcare infrastructure and research capability in underserved regions of the world. Rwanda was chosen in part due to its significant growth in mental healthcare infrastructure over a relatively short period of time.

Due to insufficient PI availability and study oversight, lack of compliance with good clinical practices, and the determination that increased sponsor operational efforts would not ameliorate the observed compliance concerns, the sponsor decided to close the pilot study early. The study closure decision was not the result of a safety signal or concern.

Based on the data collected and all accounts from investigators and site staff, the ongoing participants responded and tolerated paliperidone palmitate well. The sponsor determined it was in the best interest of the participants to continue to receive paliperidone palmitate through a post-trial access program upon study closure.

The R092670PSY4001 study met its objective in confirming that it was not possible to move forward with the open-label pragmatic study immediately following this feasibility study as originally planned unless a significant effort was made to improve research capacity. Specific capacity building and support requirements were identified during this study that will need to be implemented prior to starting, during the start-up, and throughout the conduct of the future open-label studies. Those include:

1. Improvement of site infrastructure (eg, internet access, computers, printers, and locked cabinets) to meet criteria necessary for successful clinical trial execution.
2. Improvement in site research staff resources to manage the workload of day-to-day hospital duties and clinical trial demands, which may include a full-time research coordinator, data entry person and a number of sub-investigators to act as PI backups. Specific focus should be put on ensuring PI availability in order to provide adequate study oversight.
3. Provide specialized training for site investigators on GCP, general conduct of clinical research, scientific methodology and procedures.

4. Prior to site initiation, conduct a test mock-trial with no patient involvement and no investigational product administration to ensure the sites are capable of correctly performing study procedures. After passing the mock-trial, a site can be initiated.

As the sponsor remains committed to strengthening research capabilities in Rwanda and Sub-Saharan Africa, the insights gained in collaboration with the research-naïve sites in this study will be taken into consideration when planning future studies in the region.

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LOCAL SPONSORS

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R092670 Paliperidone palmitate
Synoptic Clinical Study Report R092670PSY4001

SIGNATURE OF SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: A Pilot-Study in Rwandan Health Care Settings to Examine the Feasibility of a Large Pragmatic Clinical Study to Assess the Value of Paliperidone Palmitate in Rwanda

REPORT CONTRIBUTORS: PPD

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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: PPD

DATE: March 27th 2020

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