ILOPERIDONE

AMENDMENT NO. 4.0 TO PROTOCOL VP-VYV-683-3201

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ILOPERIDONE FOR 4 WEEKS IN THE TREATMENT OF PATIENTS WITH ACUTE MANIC EPISODES ASSOCIATED WITH BIPOLAR I DISORDER

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Sponsor: Vanda Pharmaceuticals Inc.
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Study Product: Iloperidone (VYV-683)

Protocol Number: VP-VYV-683-3201

Study Phase: III

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1. SYNOPSIS

Name of Sponsor/Company: Vanda Pharmaceuticals Inc.	
Name of Investigational Product: iloperidone	
Name of Active Ingredient: iloperidone, VYV-683	
Title of Study: A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of iloperidone for 4 weeks in the treatment of patients with acute manic episodes associated with Bipolar I Disorder	
Study center(s): Approximately 50 sites across the U.S. and Europe	
Studied period (years): Estimated date first patient enrolled: March 2021 Estimated date last patient completed (through the Short-Term Treatment Phase): May 2022	**Phase of development:** Phase III
Number of patients (planned): 400 (200 iloperidone and 200 placebo)	

Diagnosis and main criteria for inclusion:

- Meet the *Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition* (DSM-5) diagnosis of bipolar I disorder, manic or mixed type, as confirmed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID) manic or mixed type with or without psychotic symptoms
- Men and women between the ages of 18-65 years inclusive
- Had at least one prior documented manic or mixed episode (with or without psychotic symptoms) that required treatment prior to screening
- Patients with Young Mania Rating Scale (YMRS) total score ≥ 20
- Patients with ≥ 4 on at least 2 of 4 YMRS items (irritability, speech, content, disruptive/aggressive behavior)
- Patients with Montgomery-Asberg Depression Rating Scale (MADRS) total score < 18
- Voluntarily hospitalized for current manic episode

Main Exclusion Criteria:

- Patients with a DSM-5 diagnosis other than bipolar I disorder that was the primary focus of treatment within the previous six months
- Patients experiencing a first manic episode or meeting criteria for rapid cycling

Investigational product, dosage and mode of administration:
Iloperidone will be provided as overencapsulated tablets containing either 1, 3, 6, 9, or 12 mg.

Duration of treatment:
Short Term Double-Blind Treatment Phase (4 weeks)
Titration Period – 1 week
Double-Blind Treatment Period – 3 weeks

Optional Open-Label Extension Phase (52 weeks)
Open-label Titration Period – 1 week
Open-label Extension Period – 51 weeks

Reference therapy, dosage and mode of administration:
Placebo will be provided in size and appearance that are visually identical to those containing iloperidone.

Primary Objective:

To evaluate the efficacy of iloperidone monotherapy compared to placebo in the treatment of adult patients with bipolar I disorder experiencing an acute manic or mixed episode as measured by reduction in the Young Mania Rating Scale (YMRS) total score at Week 4

Secondary Objective(s):

- To evaluate the efficacy of iloperidone monotherapy compared to placebo in the treatment of adult patients diagnosed with bipolar I disorder experiencing an acute manic or mixed episode as measured by improvements in the Clinical Global Impression of Severity (CGI-S)
- To evaluate the efficacy of iloperidone monotherapy compared to placebo in the treatment of adult patients diagnosed with bipolar I disorder experiencing an acute manic or mixed episode as measured by reduction in the Young Mania Rating Scale (YMRS) total score at each trial visit
- To assess the rate of YMRS responders. A YMRS responder is defined as at least a 50% decrease from baseline in YMRS total score
- To assess the efficacy of iloperidone monotherapy compared to placebo in improving clinical symptomatology in adult patients diagnosed with bipolar disorder, manic or mixed episodes after acute treatment as measured by CGI-C
- To assess the efficacy of iloperidone monotherapy compared to placebo in improving clinical symptomatology in adult patients diagnosed with bipolar disorder, manic or mixed episodes after acute treatment as measured by MADRS
- To assess the safety and tolerability of iloperidone compared to placebo in the treatment of adult patients in an acute manic or mixed episode of bipolar I disorder as measured by changes in vital signs and weight, laboratory analytes, electrocardiograms (ECGs), and the incidence and severity of TEAEs and extrapyramidal symptoms (EPS) using the Barnes Akathisia Scale, Simpson-Angus Scale, and the AIMS

Exploratory Objective:

- To conduct a whole genome association scan to identify potential markers of response and safety for a bipolar indication

Open-label Extension (OLE) Objective:

- To explore the long-term safety and tolerability of dosing with iloperidone over an additional 52 weeks of treatment

Overall Design: This will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study has two phases: the Pre-Randomization Phase and the Short-Term Treatment Phase and is followed by an optional third phase, the Open-Label Extension (OLE) Phase. The Pre-Randomization Phase includes the Screening visit and the Baseline visit. The Short-Term Treatment Phase includes two periods: (1) the Titration Period and (2) the Double-Blind Treatment Period. The optional OLE Phase also includes two periods: (1) the OLE Titration Period and (2) the OLE Maintenance Period.

The Pre-Randomization Phase begins with the screening visit (Day -7 to -1) during which an informed consent will be obtained from potential patients and their eligibility will be initially assessed. The Screening Visit (Day -7 to -1) and Baseline Visit (Day 0) will be separated by a maximum of 1 week. Patients meeting all entry criteria for enrollment into the study will enter the Short-Term Treatment Phase. During this Phase, patients will undergo a 7-day Titration Period where iloperidone or placebo will be titrated to 24 mg/day total daily dose given as a bid regimen (12 mg bid) utilizing a fixed titration regiment, whereby the doses will be increased to 2→6→12→18→24→24→24 mg/day (bid doses of 1, 3, 6, 9, 12, 12, and 12 mg). The target dose for CYP2D6 poor metabolizers is 12mg/d (6 mg bid) utilizing a fixed titration regiment, whereby the doses will be increased to 2→6→12→12→12→12→12 mg/day (bid doses of 1, 3, 6, 6, 6, 6, and 6 mg). Patients will discontinue current antipsychotic treatment prior to the first day of the Titration Period (Day 1-7). Patients will remain in-patient during this period to ensure compliance with dosing.

Subjects continuing to meet the criteria for randomization will be eligible to proceed to the Double-Blind Treatment Period. During this period, patients will be randomized 1:1 to either iloperidone or placebo, stratified by country. Subjects will remain in this period for up to 3 weeks.

Subjects who complete the Double-Blind Treatment Period will be eligible to participate in the optional OLE Phase. Eligible subjects will enter the 7-day OLE Titration Period where iloperidone will be titrated to 24 mg/day total daily dose given as a bid regimen (12 mg bid). The target dose for CYP2D6 poor metabolizers is 12mg/d (6 mg bid). Subjects will then enter the OLE Maintenance Period in which subjects will be treated with iloperidone for up to 52 weeks.

Criteria for evaluation:

Mean baseline-to-endpoint change in total score using following parameters:

Efficacy:

- Young Mania Rating Scale (YMRS)
- Overall and mania severity of illness for Clinical Global Impression of Severity (CGI-S)
- Clinical Global Impression of Change (CGI-C)
- Montgomery-Asberg Depression Rating Scale (MADRS)

Safety:

- Adverse Events (AEs) and proportion of patients withdrawing due to AEs
- EPS scale scores as measured by Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS)
- Metabolic risk factors, clinical chemistry, hematology, vital signs, and weight
- Columbia Suicide-Severity Rating Scale (C-SSRS)
- CYP2D6 genotyping
- 12-lead electrocardiograms (ECG)

Statistical methods:

If not otherwise specified, statistical significance is defined as $p \leq 0.05$ and is two-tailed when appropriate. Data base lock will occur after 4-week ST double-blind period. The primary efficacy variable is the change from baseline in the YMRS total score.

11. STATISTICAL PLAN

11.1. Sample Size and Accrual

Based on a two-sided t-test with the 5% significant level, the planned sample size of 200 subjects per arm (a total of 400 subjects) provides around 90% power to detect a mean difference of 3.6 in YMRS (change from baseline at week 4) assuming a standard deviation of 11 in each treatment group.

11.2. Statistical Methods

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in a statistical analysis plan (SAP), which will be finalized prior to unblinding. Any changes in the statistical methods described in this protocol that occur prior to unblinding will be documented in the statistical analysis plan and will not require a protocol amendment.

11.2.1. General

Statistical analyses will be performed using two-sided tests at alpha level of 0.05.

Data will be summarized by treatment group (and by visit when applicable), with respect to demographic and baseline characteristics, efficacy variables, and safety variables.

Summary statistics will include the mean, N, standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

For the analyses of change from baseline, only patients with a baseline and at least one post-baseline measure will be included in the analysis. Unless otherwise specified, baseline is defined as the latest non-missing observation across all the visits in the screening phase, before the active study drug begins. Endpoint will be the latest non-missing observation across all the post-baseline visits in the treatment phase.

Low enrolling sites will be pooled for analysis and the pooling algorithm will be determined prior to breaking the blind. The goal of pooling low enrolling sites is to have a sufficient number of patients per treatment group within a site for the analysis models. Unless otherwise specified, the pooled sites will only be used in the analyses where the site has an effect. The actual sites rather than the pooled sites will be specified in the data listings.

Details of the model and the analyses will be specified in the SAP. All statistical analyses will be performed using SAS®, Version 9.1.3 or higher.

11.2.2. Patient Populations for Analysis

The following analysis populations will be defined for this study:

Intent-to-Treat: will include any patient randomized into the study that receives a dose of study drug and that has completed at least one post-baseline efficacy measurement while on study medication;

Safety: Any patient randomized into the study that receives a dose of study drug;

Per-Protocol: Any patient who is randomized and receives the protocol required study drug exposure and required protocol processing.

Efficacy analyses will be performed on the Intent-to-Treat population and the Per-Protocol population. Safety summaries will be based on Safety set. Patient characteristics will be presented for all patients randomized.

11.2.3. Patient Disposition

Study completion and reasons for discontinuation for all randomized patients in the treatment phase will be summarized for each treatment group. Discontinuations by reason will be tabulated for each treatment group.

As needed, time to discontinuation due to adverse events, lack of efficacy and for any reason may be analyzed using Kaplan-Meier survival techniques; the log-rank test may be used for group comparison.

11.2.4. Demography and Other Baseline Data

Demographic data and patient characteristics at screening/baseline will be listed and summarized by treatment group for all randomized patients using descriptive statistics.

Past and current medical history will be summarized by treatment group using the system organ class (SOC) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Past medical conditions will be defined as an onset date prior to randomization (Visit 2) and resolved (not on-going) as of Visit 2. Current medical conditions, defined as an onset date on or after the date of randomization (Visit 2) or an onset date prior to randomization (Visit 2) and unresolved (on-going) as of Visit 2, will be reported separately, but similarly to the past medical conditions. If both a past and a current (on-going) medical condition record are indicated for a condition, the condition will be presented under current medical conditions only.

11.2.5. Study Medication

The number of subjects at each visit will be summarized by treatment group.

The compliance to study medication, as recorded in the CRF, will also be summarized by treatment group. The proportion of subjects who are significantly noncompliant in the double-blind phase will be summarized by treatment groups.

11.2.6. Prior/Concomitant Therapy

Any medications or therapy present before the first dose of study medication (Visit 2) will be considered as prior medications. Concomitant medications (medications present while on study medication) will be recorded throughout the study and at early discontinuation. These medications will be coded using the WHO-drug dictionary. The number of subjects from the

Safety Population using prior or concomitant medications will be categorized by the WHO-drug category and preferred term, and presented for each treatment group. In any given category (e.g., drug category) a subject will be counted only once.

11.3. Efficacy Data Analysis

11.3.1. Primary Outcome

The primary efficacy outcome measure is the change from baseline in the Young Mania Rating Scale (YMRS) total score at Week 4. The primary statistical method will be mixed effect model repeat measurement (MMRM). A detailed description of the primary analysis model, and other supportive analyses will be included in the SAP.

As stated previously, any changes in the statistical methods that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

11.3.2. Secondary Outcomes

The other secondary efficacy outcomes include:

- Responder
- CGI-S
- CGI-C
- MADRS

These outcomes will be analyzed similarly as the primary outcome. The categorical endpoints will be analyzed by a Cochran-Mantel-Haenszel test with adjusting for sites.

11.4. Safety Evaluation

The primary assessment of safety will be based on the frequency of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and on the frequency of clinically notable abnormal vital signs, electrocardiograms (ECGs) and laboratory values. Other safety evaluations include changes in vital signs, changes in clinical laboratory evaluations, and changes in ECGs, extra pyramidal symptoms (EPS) using the Barnes Akathisia Scale, Simpson-Angus Scale and the AIMS, physical exam findings during treatment, and suicide ideation (C-SSRS) and behavior events.

11.4.1.1. Adverse Events

Adverse events will be recorded throughout the study and at early discontinuation. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent adverse events will be defined as those events, which are newly occurring or worsening from baseline. In all cases only treatment emergent adverse events will be summarized.

Treatment-emergent adverse events will be summarized within each treatment group by primary system organ class and preferred term. (NOTE: In any given category [e.g. body system] a patient will only be counted once.) The incidence rates of TEAEs will be analyzed as described in the SAP. Similar displays will be provided for SAE and prior (conditions ending prior to the first dose of study medication) and current (conditions present while on study medication) medical conditions.

Adverse events will further be categorized by severity, relationship to study medication, and action taken. Other information collected will be listed, as appropriate. Any event starting more than 3 days after the final dose of study medication will be excluded from the above tables and only listed, unless the event caused discontinuation.

The proportions of patients experiencing SAEs and AEs resulting in discontinuation from the study will be summarized by treatment groups.

11.4.1.2. Laboratory Data

Clinical Laboratory Data

The summary statistics of raw data (hematology and chemistry) and change from baseline values will be presented, as well as shift tables from baseline to post-baseline values using normal ranges. For urinalysis parameters, the number and percentage of patients falling under each category of the test will be presented.

Clinical laboratory data will be summarized for each treatment group by presenting the proportions of patients with clinically notable abnormalities (Appendix 17.2).

Clinically notable values will be identified according to the criteria identified in the FDA's "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates" (Revised 2-APR-87) provided by the FDA Division of Neuropharmacological Drug Products (DNDP). Differences in incidence rates between the treatment groups will be tested as described in the SAP.

11.4.1.3. Vital Signs

Data from vital signs and body measurements will be listed, clinically notable values (Appendix 17.3) will be flagged, and any other information collected will be listed. Data will also be summarized by treatment group using mean change from baseline and proportions of patients with values outside the normal range, and values that were clinically notable.

11.4.1.4. Electrocardiogram (ECG)

Results from the ECG will be listed for each patient. These data will also be summarized for each treatment group by presenting patients with newly occurring or worsening ECG abnormalities.

11.4.1.5. Extrapyramidal Symptoms (EPS)

The observed value and change from baseline in AIMS, BAS and SAS will be tabulated by treatment and analyzed by ANCOVA. In addition, categorical responses, such as “worsened”,

"unchanged" and "improved" may be derived from the AIMS, BAS or SAS scores and be compared between the two treatments. Details of the analysis will be provided in the SAP.

11.4.1.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be listed for each patient. These data will also be summarized by treatment group and for suicidal ideation events, suicidal behaviors and completed suicides. In particular, for each of the following suicide related events, the number and percent of patients with the event will be enumerated by treatment group: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, non-specific active suicidal thoughts, and wish to be dead. Details of the analysis will be provided in the SAP.

11.5. Subgroup Analysis

The subgroup analysis (such as, sex, age, baseline illness severity etc.) for efficacy variables and safety variables may be conducted as described in the SAP.

11.6. Deviations in Analysis from Statistical Plan and Other Issues

During the analysis and reporting process, any deviations from the statistical plan designed for this protocol will be described and justified in the final report.