1. TITLE PAGE

STATISTICAL ANALYSIS PLAN (SAP)

A Phase II Study of PDC-1421 Capsule to Evaluate the Safety and Efficacy in Patients with Major Depressive Disorder

Protocol No.: BLI-1005-002

First subject first visit: May-19-2015

Last visit of the study: Mar-18-2019

Sponsor: BioLite, Inc.

CRO: Virginia Contract Research Organization Co., Ltd.
3F, No. 2, Lane 258, Ruiguang Rd., Neihu District,
Taipei 114, Taiwan

Final

Date of issue: June-14-2019

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BMI	Body mass index
C.I.	Confidence interval
CRF	Case report form
CRO	Contract research organization
DRCSU	Depression Research Clinic at Stanford University
FDA	Food and Drug Administration
GCP	Good clinical practice
IQR	Inter-quartile range
IRB	Institutional review board
ITT	Intent-to-treat
LCGMH	Linkou Chang Gung Memorial Hospital
LOCF	Last observation carried forward
PP	Per-protocol
Q1	The first quantile (the 25^{th} percentile)
Q3	The third quantile (the 75^{th} percentile)
TSGH	Tri-Service General Hospital
TVGH	Taipei Veterans General Hospital
SAE	Serious adverse event
SD	Standard deviation
WH	Wanfang Hospital
VCRO	Virginia contract research organization

4. PROTOCOL AMENDMENTS

The version of approval protocol after enrolling the first subject was described as follow: As no patient were enrolled in Taipei City Hospital, Songde Branch, the site will not be included for analysis.

Approved date / Approved by	Final (version:<protocol version>)	Amendment 01 (version: <protocol version>)
TFDA	20150727 (Version 1.4)	20160630 (Version 1.5)
CGMH-LK	20150728 (Version 1.4)	20160511 (Version 1.5)
TVGH	20150806 (Version 1.4)	20160706 (Version 1.5)
TFDA	20160630 (Version 1.5)	20160910 (Version 2.0)
CGMH-LK	20160511 (Version 1.5)	20160824 (Version 2.0)
TSGH	20160802 (Version 1.5)	20161017 (Version 2.0)
TVGH	20160706 (Version 1.5)	20161104 (Version 2.0)
TFDA	20160910 (Version 2.0)	20170517 (Version 2.1)
CGMH-LK	20160824 (Version 2.0)	20170406 (Version 2.1)
TSGH	20161017 (Version 2.0)	20170512 (version 2.1)
TVGH	20161104 (Version 2.0)	20170524 (Version 2.1)
WFH	20161007 (version 2.0)	20170411 (Version 2.1)
TFDA	20170517 (Version 2.1)	20171030 (Version 2.2)
CGMH-LK	20170406 (Version 2.1)	20171113 (Version 2.2)
TSGH	20170512 (version 2.1)	20171128 (Version 2.2)
WFH	20170411 (Version 2.1)	20170411 (Version 2.2)
TFDA	20171030 (Version 2.2)	20190218 (Version 2.3)
CGMH-LK	20171113 (Version 2.2)	20190214 (Version 2.3)
TVGH	20170524 (Version 2.1)	20190318 (Version 2.3)
WFH	20170411 (Version 2.2)	20190331 (Version 2.3)
FDA	20170225 (Version 2.1)	20180513 (Version 2.3)
Stanford	20170128 (Version 2.1)	20180503 (Version 2.3)

This protocol amendment about the statistical analysis is consisted of the following (compared to the final approved protocol):

Page	Before version： 1.4	Page	Content after modification Version：1.5
2	<u>Primary endpoint</u> Change in Montgomery-Åsberg Depression	2	<u>Primary endpoint</u> Change in Montgomery-Åsberg Depression

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	Rating Scale (MADRS) total score from baseline to week 4 compared to placebo. <u>Secondary endpoint</u> • Change in Hamilton Rating Scale for Depression (HAM-D-17), Hamilton Rating Scale for Anxiety (HAM-A), Depression and Somatic Symptoms Scale (DSSS), Clinical Global Impression Scale (CGI) total score from baseline to week 2, 4 and 5. • Change in MADRS total score from baseline to week 2 and 5. • Percentage of partial responders (defined as a participant with a 25-50% decrease from baseline in total score) and responders (defined as a participant with ≧ 50% decrease from baseline in total score) in MADRS by week 2, 4 and 5. • Evaluate Safety Assessments and Columbia-Suicide Severity Rating Scale (C-SSRS) from screening stage to the last visit • Difference in the mean changes of MADRS, HAM-D-17, HAM-A, DSSS, CGI and C-SSRS from the baseline to week 2, 4 and 5 between the PDC-1421 Capsule and placebo groups.		Rating Scale (MADRS) total score from baseline to week 6 compared to placebo. <u>Secondary endpoint</u> • Change in MADRS total score from baseline to week 2 and 7. • Change in Hamilton Rating Scale for Depression (HAM-D-17), Hamilton Rating Scale for Anxiety (HAM-A), Depression and Somatic Symptoms Scale (DSSS), Clinical Global Impression Scale (CGI) total score from baseline to week 2, 4, 6 and 7. • Percentage of partial responders (defined as a participant with a 25-50% decrease from baseline in total score) and responders (defined as a participant with ≧ 50% decrease from baseline in total score) in MADRS by week 2, 4, 6 and 7. • Evaluate Safety Assessments and Columbia-Suicide Severity Rating Scale (C-SSRS) from screening stage to the last visit • Difference in the mean changes of MADRS, HAM-D-17, HAM-A, DSSS, CGI and C-SSRS from the baseline to week 2, 4, 6 and 7 between the PDC-1421 Capsule and placebo groups.
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			mean body weights, mean body weight gains and food consumption in all treatment groups were noted. In clinical pathology, no toxicity evidences were noted for all parameters (hematology, serum chemistry and urinalysis), no treatment-related gross abnormality was found at necropsy, and no significant toxicity evidences in organ weights evaluation. And the histopathological findings showed that no treatment-related changes in vehicle control and PDC-1421 treated groups. It was estimated that the NOAEL of PDC-1421 of the 13-week repeated dose toxicity study is 2500 mg/kg/day for both males and females.
22	As Page 2	22	As Page 2
24	3.5.4 Dosing Regimen, packing and labeling Table 14. Summary of dosing regimen Visits of Part II Biweekly for 28 days	24	3.5.4 Dosing Regimen, packing and labeling Table 14. Summary of dosing regimen Visits of Part II Biweekly for 42 days
25	In part II, eligible subjects are randomized into one of three treatment arms in a 1:1:1 ratio [one capsule of PDC-1421 Capsule and placebo thrice daily; two capsules of PDC-1421 Capsule thrice daily; two capsules of placebo thrice daily] for 28 days. After the two weeks of drug administration, subjects will return to the center for assessments then get another study drug bag for the following 14 days. The biweekly clinic visits are two times and one week later after the last dose for follow-up. Investigational drug (PDC-1421 Capsule or placebo) are provided by BioLite, Inc. and stored in Department of Pharmacy, Taipei Veterans General Hospital, Linkou Chang Gung Memorial Hospital and Taipei City		In part II, eligible subjects are randomized into one of three treatment arms in a 1:1:1 ratio [one capsule of PDC-1421 Capsule and placebo thrice daily; two capsules of PDC-1421 Capsule thrice daily; two capsules of placebo thrice daily] for 42 days. After the two weeks of drug administration, subjects will return to the center for assessments then get another study drug bag for the following 14 days. The biweekly clinic visits are three times and one week later after the last dose for follow-up. Investigational drug (PDC-1421 Capsule or placebo) are provided by BioLite, Inc. and stored in Department of Pharmacy, Taipei Veterans General Hospital, Linkou Chang Gung Memorial Hospital, Taipei City

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21	3.1 General Design The targeted population of this study is 72 subjects who met the per-protocol basis, in which 12 are assigned to part I, 60 are assigned to part II.	21	3.1 General Design The targeted population of this study is 72 subjects who met the intent-to-treat (ITT) basis, in which 12 are assigned to part I, 60 are assigned to part II.

Page	Before version： 2.1	Page	Content after modification Version：2.2
48	8.1 Sample Size Determination Based on our study design, it is planned to enroll 60 subjects who met the per-protocol basis.	48	8.1 Sample Size Determination Based on our study design, it is planned to enroll 60 subjects who met the intent-to-treat (ITT) basis.

Page	Before version： 2.2	Page	Content after modification Version：2.3
42	The total score is used to define treatment response (≧40% reduction from baseline) and partial response (20-39% reduction from baseline).	42	Percentage of partial responders (defined as a participant with a 25-50% decrease from baseline in total score) and responders (defined as a participant with ≧50%decrease from baseline in total score.

5. INVESTIGATIONAL PLAN

5.1 Objective

5.1.1 Primary objective

The primary objective of this trial was to determine the effective doses and treatment period of PDC-1421 Capsule in subjects with MDD.

5.1.2 Secondary objective

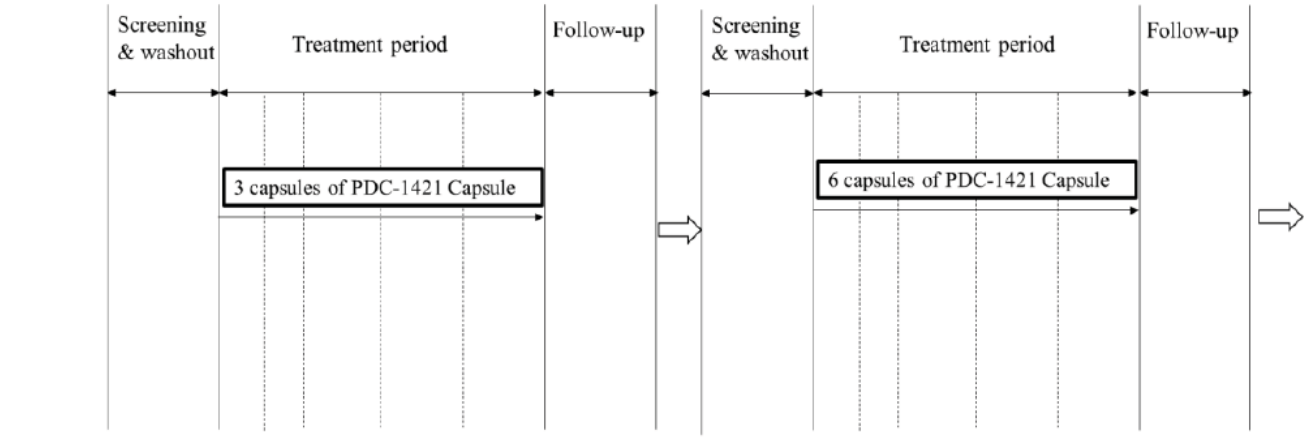
To evaluate the safety of PDC-1421 Capsule in subjects receiving PDC-1421 at various dose levels .

5.2 Study Design

The screening phase is intended for diagnosing and assessing the patient for possible inclusion in the study and for providing an adequate washout period. The following study will be conducted in two parts. The targeted population of this study is 72 subjects who met the intent-to-treat (ITT) basis, in which 12 are assigned to part I, 60 are assigned to part II. Part I is an open-label study, multiple center and dose escalation evaluation in twelve patients. Six subjects each will be evaluated for any safety concerns at 1 or 2 capsules TID dose for 28 days, sequentially. Each of them will be assessed twice in the first week after administration of PDC-1421 Capsules and once a week in the following treatment. Part II is a randomized, double-blind, placebo-controlled, parallel-group study. 60 subjects will be randomly assigned on a 1:1:1 basis to one of the three treatment arms (1 PDC-1421 Capsule plus 1 placebo TID, 2 PDC-1421 Capsule TID, 2 placebo TID) for 6 weeks (42 days) and evaluated the safety and efficacy every two weeks during the treatment period. The performance of PDC-1421 Capsule on MDD subjects will provide us with valuable information for our next phase of the study.

5.2.1 Schematic Diagram of The Study:

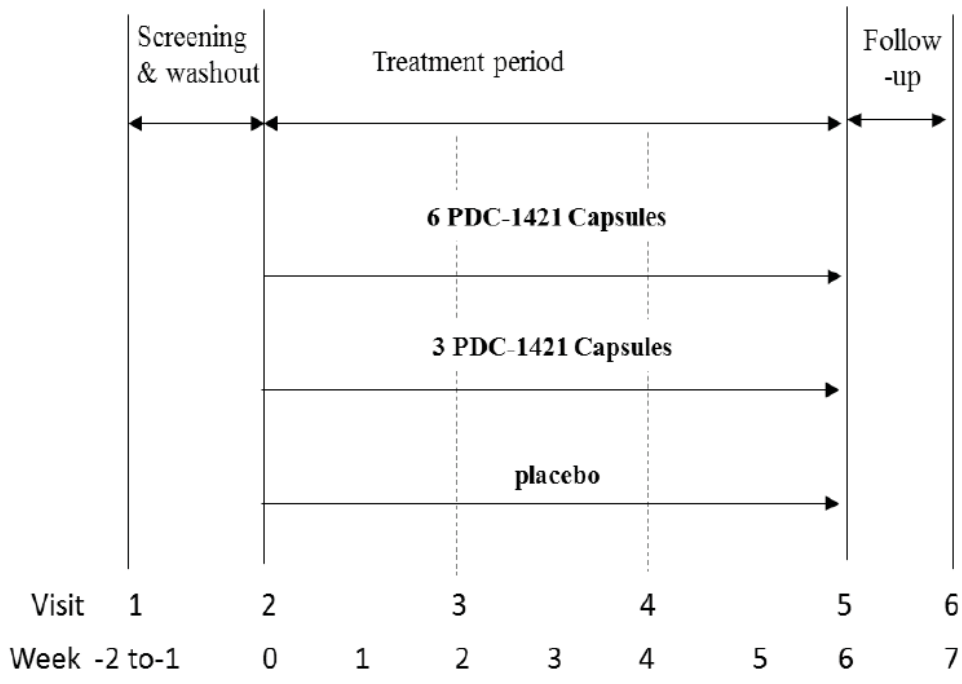
Part I.



* Subjects are assessed once between visit 2 and 4

⇨ Checkpoints

Part II.



5.2.2 Study Medication Administration

In part I, six subjects each will take 1 or 2 capsules thrice daily for 28 days, sequentially. Subjects are assessed twice in the first week after drug administration and they will receive the study drug bag for the following 7 days every week. In part II, eligible subjects are randomized into one of three treatment arms in a 1:1:1 ratio (one capsule of PDC-1421 Capsule and placebo thrice daily; two capsules of PDC-1421 Capsule thrice daily; two capsules of placebo thrice daily) for 42 days. After the two weeks of drug administration, subjects will return to the center for assessments then get another study drug bag for the following 14 days. The biweekly clinic visits are three times and one week later after the last dose for follow-up.

5.2.3 Flowchart of study procedures

Part I-schedule of assessments

*On ±2 days.

*V3 (Week 1/2) only can be conducted in Day 3 or Day 4.

	Screening	Treatment Period						Follow-up
Visit	1	2	3	4	5	6	7	8
***Week**	-2 to -1 ~0	0	1/2	1	2	3	4	5
Informed consent	•							
Subject information	•							
Medical history	•	•						
DSM-IV-TR	•							
HAM-D-17	•	•		•	•	•	•	•
CGI	•	•		•	•	•	•	•
MADRS	•	•		•	•	•	•	•
DSSS	•	•		•	•	•	•	•
HAM-A	•	•		•	•	•	•	•
C-SSRS	•	•	•	•	•	•	•	•
Concomitant medication	•	•	•	•	•	•	•	•
Physical examination	•	•	•	•	•	•	•	•
Vital sign	•	•	•	•	•	•	•	•
ECG	•	•	•	•	•	•	•	•
Laboratory examination								
Drug screen	•							
Pregnancy test	•							•
Hematology	•	•			•		•	•
Blood chemistry	•	•			•		•	•
Eligibility evaluation	•							
Drug accountability		•	•	•	•	•	•	
AE/SAE evaluation			•	•	•	•	•	•

Part II-schedule of assessments

*On ±2 days.

** If the interval of visit 1 and visit 2 is within 7 days, Hematology and Blood

chemistry test of visit 2 can be skipped.

	Screening	Treatment Period				Follow-up
Visit	1	2	3	4	5	6
*Week	-2 to -1 ~ 0	0	2	4	6	7
Informed consent	•					
Subject information	•					
Medical history	•	•				
DSM-IV-TR	•					
HAM-D-17	•	•	•	•	•	•
CGI	•	•	•	•	•	•
MADRS	•	•	•	•	•	•
DSSS	•	•	•	•	•	•
HAM-A	•	•	•	•	•	•
C-SSRS	•	•	•	•	•	•
Concomitant medication	•	•	•	•	•	•
Physical examination	•	•	•	•	•	•
Vital sign	•	•	•	•	•	•
ECG	•	•	•	•	•	•
Laboratory examination						
Drug screen	•					
Pregnancy test	•					•
Hematology	•	•**	•	•	•	•
Blood chemistry	•	•**	•	•	•	•
Eligibility evaluation	•					
Drug accountability		•	•	•	•	
AE/SAE evaluation			•	•	•	•

5.3 Statistical Methods Planned in the Protocol and Determination of Sample Size

5.3.1 Populations for analysis

The efficacy measures are conducted on the per-protocol (PP) and intent-to-treat (ITT) basis. The per protocol will be defined as (1) The drug compliance is at least 80% (2) Subjects have completed data to determine the primary endpoint. (3) Subjects cannot have protocol deviation. The protocol deviation will be defined as (1) Inclusion or exclusion criteria not satisfied. (2) Not permitted concomitant medications (3) Wrong randomized treatment prescribed. An intent-to-treat (ITT) basis will be defined as the data are analyzed by the treatment groups to which the randomized patients who take at least one dose of study medication and have any post-baseline safety data collected.

The safety measures are conducted on the ITT basis.

5.3.2 Endpoints

Primary endpoint:

In part II, the primary endpoint is the change of Montgomery-Å sberg Depression Rating Scale (MADRS) total score from baseline to Week 6 compared to placebo.

Secondary endpoints are:

- MADRS total score－change from baseline to week 2 and 7
- HAM-D-17, CGI, DSSS and HAM-A－change from baseline to week 2, 4, 6 and 7
- Percentage of partial responders and responders (defined as participants with a 25-50% decrease and a ≧50% decrease from baseline in total score, respectively) in MADRS total score by Week 2, 4, 6 and 7
- Difference in the mean changes of MADRS, HAM-D-17, HAM-A,DSSS, CGI and C-SSRS from baseline to week 2, 4, 6 and 7 between PDC-1421 Capsule and placebo groups.

Safety endpoints:

- physical examination
- vital signs
- laboratory data (blood chemistry)
- ECG
- Columbia-Suicide Severity Scale (C-SSRS)
- Incidence of AE/SAE

5.3.3 Statistical Evaluation

Simple descriptive statistics with 95% confidence interval will be performed with data collected in this study wherever applicable. Treatment effects are evaluated based on 2-sided test with a 0.05 significant level. All data shall be tabulated and presented in the study report. The descriptive statistics will be provided. The safety and efficacy data will be analyzed using the non-parametric method.

5.3.3.1 Primary analysis methods

The efficacy and safety information recorded on CRF will be summarized by tables presented in frequency and percentage for categorical variables, in mean with SD as well as median with the minimum and maximum for continuous variables. The comparison between three groups will be analyzed by nonparametric method as appropriate. All adverse events will be summarized with coding term, severity, relationship to study drug by frequency tables with the counts and percentage. In addition, serious adverse events will be listed with event narration.

5.3.4 Determination of sample size

In part I, six subjects each will be evaluated for safety and efficacy assessments at 1 or 2 capsules TID dose for 28 days, sequentially.

In part II, this is a small proof-of-concept study to evaluate 2 doses of PDC-1421 and placebo in the treatment of major depressive disorder. Based on our study design, it is planned to enroll 60 subjects who met the intent-to-treat (ITT) basis.

5.4 Changes in the Conduct of the Study or Planned Analyses

All the statistical analysis will follow protocolized statistical contents.

6. STATISTICAL EVALUATIONS

The statistical objective of this study is to assess the safety and efficacy profiles in three groups - 1 PDC-1421 capsule plus 1 placebo, 2 PDC-1421 Capsule, and 2 placebos.

6.1 Data Sets Analyzed

Two study populations are intention-to-treat (ITT) population and per-protocol (PP) populations which are defined in section 5.3.1.

The efficacy evaluations will be performed on both of the ITT and PP datasets while the safety evaluations will be performed on the ITT dataset. The primary conclusion will be made for the primary endpoint on the ITT population

Demographic and baseline (Visit 2) characteristics will be performed on the ITT population.

Sample size, mean, 95% confidence interval of mean, median, standard deviation, inter-quartile range, maximum and minimum will be summarized for continuous variables. For categorical variables, the frequency and percentage will be provided.

6.2 Demographics and Other Baseline Characteristics

Demography and baseline characteristics will be summarized in descriptive statistics and listed by part, center and treatment.

6.2.1 Demographic data

Demographic variables including age(year), height (cm), weight (kg) and BMI (kg/m^2) will be summarized. Subjects' gender will be tabulated.

Age (years) = integer of (date of initial visit – date of birth) / 365.25

BMI (Kg/m^2) = (weight) / $(height)^2$ rounds to one decimal place

6.2.2 Major Depressive Disorder History and Medical history

Frequency table of Diagnosis and Statistical Manual of Mental Disorders-IV, text revision (DSM-IV-TR) will be presented.

Frequency table of subject with medical history and current medical condition will be presented.

General medical history will be presented in incidence table and listed for each subject. Ongoing medical conditions will be presented separately from the cured diseases.

6.2.3 Concomitant medications

Frequency table of subjects with pre-treatment and concomitant medications will be presented. WHO Drug Dictionary will be applied.

Pre-treatment medications are the medications taken before the first dosing of study drug, while concomitant medications are those taken during the treatment duration (from first dosing date of study drug to the day before exiting from study).

6.3 Study Treatment Administration

6.3.1 Treatment Compliance

Subjects' compliance (%) during the treatment period will be tabulated by part, center, and treatment and calculated according to the following formula:

$$= 100* \frac{\text{Number of study medication actually took during the extent of exposure}}{\text{Number of study medication should be taken during the extent of exposure (\#)}}$$

= (number of study medication should be taken per day) * (extent of exposure, section 6.3.2)

6.3.2 Extent of Exposure

Extent of exposure (days) = date of last drug taken – date of first drug taken + 1

If the date of first drug taken is not available, the date when the drug was firstly dispensed will be used for calculation.

If the date of last drug taken is not available, the date will be replaced with that of the last drug return, previous drug taken, or previous drug return in order.

6.3.3 Mean Daily Dose

Descriptive statistics of mean daily dose of the test drug will be presented by part, center, and treatment.

$$\text{Mean daily dose} = \frac{\text{Number of study medication taken}}{\text{Extent of exposure (section 6.3.2)}}$$

6.4 Analysis of Efficacy

Results of efficacy will be presented with descriptive statistics (i.e. sample size, number of missing data, mean, 95% confidence interval of mean, median, standard deviation, inter-quartile range, maximum and minimum) for continuous parameters by part, visit, and treatment. Line charts of all efficacy outcomes will be generated and presented as mean and standard deviation.

6.4.1 Primary Efficacy Endpoint

In part II study, the primary endpoint is the net change of the MADRS total score at the 6th week after treatment (Mean MADRS total score at week 6 – Mean MADRS total score at baseline [Visit 2]).

Kruskal-Wallis test will be implemented to test the group difference.

The primary hypothesis will be:

H_0: The mean ranks of the groups are the same
H_a: The mean ranks of the groups are not the same

One a significant treatment effect is found, Wilcoxon rank sum test with Holm procedure will then be performed for comparisons between two treatment groups and the placebo group. The treatment group will be declared superior if null hypothesis is rejected and μ_{t1} and/or μ_{t2} is greater than μ_p.

6.4.2 Secondary efficacy endpoints:

In the part II study, change from baseline in MADRS at week 2/4/7, along with net changes in HAM-D-17, HAM-A, DSSS, and CGI at week 2/4/6/7 are the secondary endpoints. Also, group differences in net changes of the MADRS, CGI, HAM-D-17, HAM-A, and DSSS at the 2^{nd}, 4^{th}, 6^{th}, and 7^{th} week are the secondary efficacy endpoints. For the results with regard to MADRS and HAM-D-17, the summary of all sites in Taiwan will also be provided to contrast with the one in America.

Descriptive statistics for original and changes from baseline will be display by part, center, visit and treatment. As for the group difference, it will be examined by Kruskal-Wallis test. A significant treatment effect will be claimed after the Wilcoxon rank sum test for post-hoc tests.

In addition to the treatment difference, the effect of different product batches (or batch number)- the first batch and the second batch, on MADRS will also be examined. Drugs with batch number of "HDP-045A-040327" and placebos with batch number of "HDP-045C-040327" are classified into the first batch of product. The batch numbers included in the

second batch are "HDP-045A-070119" for PDC-1421 and "HDP-045C-070119" for placebo. Subjects with baseline visit later than 2018/02/13, or those who were enrolled before 2018/02/13 and got drugs after 2018/03/15 will be classified into the subgroup of the second batch.

The responder and partial responder is defined by the net change in total score of MADRS (responders are defined as participants with a $\geqq$50% decrease in total score from baseline; partial responders are defined as participants with at least 25% and no more than 50% decrease in total score from baseline). The percentage difference between treatment groups will be examined by Cochran-Mantel-Haenszel test.

The same definitions of partial responder will be used for HAM-D-17. The difference between the treatment will be compared with Cochran-Mantel-Haenszel test as well.

All statistical tests used will be two-tailed with α =0.05.

6.5 Analysis of Safety

6.5.1 Adverse events (AEs)

The coding system used will be the Medical Dictionary for Regulatory Activities (MedDRA).

Pre-treatment AE is the AE onset before the first dosing of study drug, while treatment-emergent AE is the one onset after the first dosing of study drug. Pre-treatment AE and treatment emergent AE will be analyzed separately.

Frequency table of subjects with pre-treatment AE (PTAE) and treatment emergent AE (TEAE) will be presented by part, center and treatment.

For TEAE, adverse event incidents will also be summarized descriptively by system organ class and preferred term using MedDRA. If more than one type of event occurred within a system organ class/ preferred term for the subject, the subject is counted only once for each system organ class/ preferred term.

For TEAE, incidence tables of severity, action taken, relationship to study drug, outcome and serious AE or not will be presented by part, center, preferred term and treatment.

The frequency distribution of severity, action taken, relationship to study drug, and outcome of all AE events will be presented by part, center, and treatment.

6.5.2 Serious adverse events (SAEs)

Incidence of serious adverse event will be tabulated. Serious adverse events incidents will be summarized descriptively by part, center, system organ class/ preferred term, and treatment group.

6.5.3 Laboratory data

Descriptive statistics of original data and net changes in hematology and biochemistry data will be presented by part, center, visit, and treatment.

Results of clinical significance with regard to laboratory data will be summarized with frequency and percentage.

6.5.4 Physical Examination (PE)

Incidence table including umber and percentage of patient with abnormal PE will be tabulated by part, center, visit, and treatment for each body system.

The corresponding body system will be analyzed and reported using a transition table. The type of transition includes no change, change to normal, change to non-clinical significance, (NCS), change to clinical significance (CS) for each body system from baseline (Visit 2).

6.5.5 Vital Signs

Descriptive statistics of net changes in vital signs including systolic and diastolic blood pressure, heart rate and body temperature will be presented by part, center, visit, and treatment.

Results of clinical significance with regard to vital sign will be summarized with frequency and percentage.

6.5.6 ECG

Frequency table and change in ECG result will be summarized by part, center, visit and treatment. The transition of ECG is define as following 4 groups: no change, change to normal, change to non-clinical significance, (NCS), change to clinical significance (CS).

6.5.7 C-SSRS

Results of C-SSRS will be presented by part, center, visit, and treatment. The baseline of C-SSRS was set at screening visit (Visit 1).

The analysis for C-SSRS will follow the official guidance "Columbia-Suicide Severity Rating Scale - Scoring and Data Analysis Guide." The 10 categories will be defined according to 10 binary responses (yes/no) on the C-SSRS, which are:

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

Suicidal ideation is identified if the total score of the five suicidal ideation questions (Categories 1-5)>0. Suicidal behavior is identified if the total score of the five suicidal behavior questions (Categories 6-10)>0. Suicidal ideation or behavior is identified if the total score of the ten suicidal ideation and behavior questions (Categories 1-10)>0.

Changes of suicidal ideation, suicidal behavior, and suicidal ideation or behavior from baseline during treatment will be summarized in a shift-table by visit, center and treatment.

6.6 Statistical / Analytical Issues

6.6.1 Adjustments for covariates

No adjustment for covariates will be performed in this study.

6.6.2 Handling of Dropouts or Missing Data

Missing data caused by premature termination will be utilized the last observation carried forward (LOCF). However, the LOCF method will only be applied to data on efficacy. No imputation will be done for safety data.

6.6.3 Interim Analyses and Data Monitoring

No interim analysis was planned.

6.6.4 Multicenter Studies

This is a multi-center study, which was conducted in the Depression Research Clinic at Stanford University, Tri-Service General Hospital, Taipei Veterans General Hospital, Linkou Chang Gung Memorial Hospital, Taipei City Hospital, Songde Branch, and Wanfang Hospital. All results will be listed by center.

6.6.5 Multiple Comparisons / Multiplicity

The Holm procedure will be carried out for the post-hoc test of the primary endpoint.

6.6.6 Use of An "Efficacy Subset" of Subjects

All analyzed populations were defined in section 5.3.1; no other population will be utilized in statistical analyses.

6.6.7 Active-Control Studies Intended to Show Equivalence

Not applicable

6.6.8 Examination of Subgroups

No subgroup analysis was conducted in the study. All center data will be pooled together for analyses of efficacy endpoint.

6.6.9 Relocation of Visit Data by Time Window

Subject with visit relocation are listed in table below:

Obs	Subject number	Visit on CRF	Real date of visit	Reallocated visit	Decision from sponsor
8	11-07-07	8	2016/04/11	7	8
14	21-07-08	6	2017/04/12	4	4
20	21-08-07	6	2017/05/03	5	5
26	21-10-10	6	2017/04/18	3	4
32	21-19-19	6	2017/12/06	3	3
38	21-26-25	6	2018/06/04	3	3
44	21-27-26	6	2018/12/01	999	3
48	22-03-02	6	2017/01/11	3	3
53	22-04-03	5	2017/02/15	6	5
59	22-06-05	6	2017/04/25	4	4
64	27-03-02	5	2018/08/07	6	5

* 999= cannot be determined

6.6.10 Random effect and fixed effect when modeling

Not applicable

6.6.11 Outliers

Outliers will not be excluded for and some extreme values will be excluded from this study.

6.6.12 Calibration of Laboratory Data Between Centers

Units of continuous laboratory data will be unified; the ones used in a plurality of center will be the standard.

7. DOCUMENTATION OF STATISTICAL METHODS

7.1 Documentation of Statistical Methods

Following SAS procedures will be applied for statistical methods mentioned in Chapter 6.

SAS procedure	**Statistical Analysis Method**	**Comment**
Freq	Frequency table	
	Cochran-Mantel-Haenszel Test	Test of association between variables by controlling for multiple centers
Sgplot	Graph	
NPAR1WAY	Kruskal-Wallis test	To test group difference of continuous variables
	Wilcoxon rank sum test	Post-hoc test
MULTTEST	Holm's Procedure	Significant level control for Multiplicity
MEANS	Descriptive Statistics	Means, SD, Min, Max, Med, IQR, P1, P3

*Center effect will be incorporated in only when degree of freedom is sufficient.

8. DATA HANDLING PROCEDURE

8.1 Coding System

The MedDRA system (version 20.0) is used to code adverse events.

Concomitant medication will be coded via WHODRUG.

General medical history term will be coded via ICD-10 coding system

8.2 Data Storage and Analysis

All data are stored in the VCROCTIS system.

Statistical evaluation will be performed using SAS 9.4 (SAS-Institute Inc., Cary, NC).

9. STUDY SUBJECTS

9.1 Disposition of Subjects

The number and percentage of randomized subject no. and analysis population will be tabulated by center and treatment.

9.2 Withdrawal of Subjects

Frequency table of the reasons for subject withdraw from study will be presented by center and treatment.

9.3 Protocol Deviations

Protocol deviations will be listed and will be tabulated by center and treatment.

10. REFERENCE LIST

Clenn A. Walker, Common Statistical Methods for Clinical Research with SAS® Examples, 2nd edition, Cary, NC, SAS Institute Inc., 2002

Shein-Chung Chow, Jen-pei Liu, Design and Analysis of Clinical Trials, John Wiley & Sons, Inc., 1998

11. APPENDICES

11.1 Normal Ranges For Laboratory Variables

Will be listed in data listings

11.2 Table of Contents (TOC) for Tables, Figures and Listing

Refer to section 14 and 16.2 in clinical study report

No further SAP amendment will be required for the deviation of TOC when the changes are still complied with the main text SAP.

11.3 Mock-up tables

Refer to attachment "MUT_BOLPDCA20141117_20180626_01_final_20190611.pdf"

11.4 Version Control Information of SAP

Document	Version	Approved date
Final	20180626_00	Apr-19-2019
Final	20180626_01	June-14-2019

11.5 Contents of Amendment of SAP

Page	Before version： 00	Page	Content after modification Version：01
20~ 21	6.4 Analysis of Efficacy Results of efficacy will be presented with descriptive statistics (i.e. sample size, number of missing data, mean, 95% confidence interval of mean, median, standard deviation, inter-quartile range, maximum and minimum) for continuous parameters by part, visit, and treatment.	20~ 21	6.4 Analysis of Efficacy Results of efficacy will be presented with descriptive statistics (i.e. sample size, number of missing data, mean, 95% confidence interval of mean, median, standard deviation, inter-quartile range, maximum and minimum) for continuous parameters by part, visit, and treatment. Line charts of all efficacy outcomes will be generated and presented as mean and standard deviation.
22	Definition of partial responder …partial responder are defined as participants with at least 25% and no more than 50% decrease in total score from baseline) and the 95% confidence interval (CI) will be computed.	22	Definition of partial responder …partial responders are defined as participants with at least 25% and no more than 50% decrease in total score from baseline).
22	6.5.1 Adverse events (AEs) For TEAE, incidence tables of severity, action taken, relationship to study drug, outcome and serious AE or not will be presented by part, center, and treatment.	22	6.5.1 Adverse events (AEs) For TEAE, incidence tables of severity, action taken, relationship to study drug, outcome and serious AE or not will be presented by part, center, preferred term and treatment. The frequency distribution of severity, action taken, relationship to study drug, and outcome of all AE events will be presented by part, center, and treatment.
23	6.5.4 Physical Examination (PE) Only when abnormality is recorded, the corresponding body system will be analyzed and reported using a transition table. The type of transition includes normal -> normal, normal -> abnormal, abnormal -> abnormal, and abnormal-> normal for each body system from baseline (Visit 2).	23	6.5.4 Physical Examination (PE) The corresponding body system will be analyzed and reported using a transition table. The type of transition includes no change, change to normal, change to non-clinical significance, (NCS), change to clinical significance (CS) for each body system from baseline (Visit 2).
23	6.5.5 Vital Signs Descriptive statistics of net changes in vital signs including systolic and diastolic blood pressure, heart rate and	23	6.5.5 Vital Signs Descriptive statistics of net changes in vital signs including systolic and diastolic blood pressure, heart rate and

	body temperature will be presented by part, center, visit, and treatment.		body temperature will be presented by part, center, visit, and treatment. Results of clinical significance with regard to vital sign will be summarized with frequency and percentage.
23	6.5.6 ECG Frequency table and change in ECG result will be summarized by part, center, visit and treatment. The transition of ECG is define as following 4 groups: normal -> normal, normal -> abnormal, abnormal -> abnormal, and abnormal-> normal.	23	6.5.6 ECG Frequency table and change in ECG result will be summarized by part, center, visit and treatment. The transition of ECG is define as following 4 groups: no change, change to normal, change to non-clinical significance, (NCS), change to clinical significance (CS).
30	11.3 Mock-up tables Refer to attachment "MUT_BOLPDCA20141117_20180626_00_final20190411.pdf"	30	11.3 Mock-up tables Refer to attachment "MUT_BOLPDCA20141117_20180626_01_final_20190611.pdf"