NCT Number: NCT0269908

Statistical Analysis Plan (SAP)

A Phase II Tolerability and Efficacy Study of PDC-1421 Treatment in Adult Patients with Attention-Deficit Hyperactivity Disorder (ADHD), Part I

PROTOCOL NUMBER	BLI-1008-001
STUDY MEDICATION	PDC-1421 Capsule
SPONSOR	BioLite, Inc. 2F, No. 20, Sec. 2, Shengyi Rd., Zhubei City, Hsinchu County 30261, Taiwan
DATE	17 Aug. 2020
VERSION	2.0

Comparison Table of SAP

Original version: 1.0; Date: 2020/05/07.

Revised version: 2.0; Date: 2020/08/17.

Changed items and pages (new version)	Version 1.0 Date: 2020/05/07	Version 2.0 Date: 2020/08/17	Reasons
All pages version	Statistical Analysis Plan, Version: 1.0 BLI-1008-001_protocol_v1.9_2020/01/15 Date: 7 May 2020	Statistical Analysis Plan, Version: 2.0 BLI-1008-001_protocol_v2.0_2020/06/30 Date: 17 Aug. 2020	Version changed
Page 9 Protocol Number	BLI-1008-001 (Version 1.9)	BLI-1008-001 (Version 2.0)	Due to protocol amendment
Page 14 3. Study Design	The targeted population of this Part I study is six subjects who met the per-protocol basis.	The targeted population of this Part I study is six subjects who met the ~~per-protocol~~ intent-to-treat basis.	
Page 16 6.2 Treatment Schedule	(None)	Add the statement "During the COVID-19 public health emergency, the assessments of CAARS, CGI, ADHDRS, C-SSRS, AE evaluation, Concomitant Medication, Physical examination can be conducted by telephone, video, or email, but those remote assessments should be documented."	
Page 18~19 7. Protocol Versions and Protocol Amendments	(None)	Add "Version 2.0" and "2020/06/30". Add the summary of statistical changes for protocol version 2.0.	
Page 19 9.1 Age (years)	(None)	Add the statement "Round down to an integer."	Specifying the definition more clearly
Page 20 9.5 CAARS-S:S	The *T*-scores of the subscales will be online calculated by a tool from Multi-Health Systems Inc. Online Assessment Center[+].	The statement is deleted.	Due to the sponsor's decision

Changed items and pages (new version)	Version 1.0 Date: 2020/05/07	Version 2.0 Date: 2020/08/17	Reasons
Page 25 10.7.2 Secondary Efficacy Analyses	The *T*-scores of CAARS-S:S will be assessed for each visit change from baseline (V3-V2, V4-V2,⋯,V8-V2) by Wilcoxon signed-rank test.	The *T*-scores of CAARS-S:S (Conners et al. 1999) will be assessed for each visit change from baseline (V3-V2, V4-V2,⋯,V8-V2) by Wilcoxon signed-rank test.	Specifying the reference of *T*-scores' calculation
Page 28 12. Reference	(None)	Add the reference "Conners, C. K., Erhardt, D., & Sparrow, E. P. (1999). Conners' adult ADHD rating scales (CAARS): technical manual. North Tonawanda, NY: Multi-Health Systems."	
Table T09.2~T09.3	(None)	Indent the sub-items of "Relation to Study Drug"	Being easier to read
Listing	Listing L01.2: Listing of Protocol Deviation / Violation	The listing is deleted.	This should not be stated in SAP.
Listing	Listing L01.3	Listing L01.2	Recoding the number
Listing	Listing L01.4	Listing L01.3	
Listing L10.1~L10.2	The content was presented as string.	The content is presented as number and the footnotes are added.	Due to the sponsor's decision
Listing L11	The content was presented as string.	The content is presented as number and the footnotes are added.	
Listing L12.1~L12.3	The content was presented as string.	The content is presented as number and the footnotes are added.	
Listing L13.1	*(SAP, 9.6.3)	*The number of item is coded in SAP, 9.6.3.	Specifying the description more clearly
Listing L13.2	The content was presented as string.	The content is presented as number and the footnotes are added.	Due to the sponsor's decision
Listing L16.1~L16.2	(None)	Add the column "Series No."	Distinguishing the data from different time for each subject
Listing L17.1~L17.2	(None)	Add the column "Series No."	

Signature Page

SAP Author:

Wen-Jin Guo
Institute of Population Health Sciences, National Health Research Institutes

Signature: Wenjin Guo
Date (DD/MMM/YYYY): 18/Aug/2020

SAP Reviewer:

Chin-Fu Hsiao
Deputy Director,
Institute of Population Health Sciences, National Health Research Institutes

Signature:
Date (DD/MMM/YYYY): 18/Aug/2020

Sponsor:

Chi-Hsin R. King
CSO,
New Drug Development Division, BioLite, Inc.

Signature: Chi-Hsin R. King
Date (DD/MMM/YYYY): 18/Aug/2020

Abbreviations and Definitions of Terms

Abbreviation	Term
Abn. w S.	Abnormal with significance
Abn. w/o S.	Abnormal without significance
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV
ADL	Activities of Daily Living
AE	Adverse Event, whether or not considered related to the investigational drug, must be recorded in CRF.
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
C#	Category # (e.g. 'C6' means 'Category 6')
C-SSRS	Columbia-Suicide Severity Rating Scale
CAARS-S:S	Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version
CGI-ADHD-I	Clinical Global Impression-Attention-Deficit/Hyperactivity Disorder-Improvement
CGI-ADHD-S	Clinical Global Impression-Attention-Deficit/Hyperactivity Disorder-Severity
Clinical monitor	The designated CRA monitoring this study for the sponsor
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	The Electrocardiogram (ECG) is a graphical recording of the cardiac cycle produced by an electrocardiograph.
HCG	Human chorionic gonadotropin
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio

Abbreviations and Definitions of Terms

Abbreviation	Term
IR	Infrared
ITT	Intent-to-Treat
LDH	Lactate Dehydrogenase
LDL	Lower-Density Lipoprotein
NLT	Not Less Than
NMT	Not More Than
p.o.	By mouth or orally
PP	Per-protocol
P.R.N.	*pro re nata*, a Latin phrase meaning "as needed."
PT	Prothrombin time
QTc	Q-T Interval Corrected For Heart Rate
RBC	Red Blood Cell
SAE	Serious Adverse Event, whether or not considered as related to the investigational drug must be recorded and reported.
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
Study Cohort	The Study Cohort is defined as a group or cohort of subjects who are assigned to take the same dose level of the study drug.
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TID	Three times a day
TLC	Thin Layer Chromatography
TSH	Thyroid-stimulating hormone
UV	Ultraviolet
V#	Visit # (e.g. 'V6' means 'Visit 6')
WBC	White Blood Cell

Table of Contents

Table of Contents

1. Protocol Summary

Name of Sponsor	BioLite, Inc.
Name of Finished Product	PDC-1421 Capsule
Name of Active Ingredient	PDC-1421
Study Title	A Phase II Tolerability and Efficacy Study of PDC-1421 Treatment in Adult Patients with Attention-Deficit Hyperactivity Disorder (ADHD), Part I
Clinical Trial Phase	II
Protocol Number	BLI-1008-001 (Version 2.0)
Principal Investigator	Dr. Keith McBurnett
Study Site	University of California San Francisco (UCSF) Medical Center
Study Period	1 year
Study Objectives:	
Primary Study Objective	To determine the efficacy profile of PDC-1421 Capsule in ADHD with ADHD Rating Scale-IV (ADHD-RS-IV).
Secondary Study Objective	To determine the efficacy and safety profile of PDC-1421 Capsule in ADHD with other rating scales.
Methodology:	
Study Design	Part I: open label, dose escalation study
Number of Subjects	Maximum 6 subjects
Duration of treatment	56 days
Study Intervention	The screening phase is intended for diagnosing and assessing the patient for possible inclusion in the study and for providing an adequate washout period. Part I is an open-label study, single center and dose escalation evaluation in six subjects. Six subjects will be initially evaluated for safety and efficacy assessments at low-dose (1 capsules TID) for 28 days. A safety checkpoint will be evaluated at day-28 for entering the high-dose (2 capsules TID). The subjects who pass the checkpoint will be initially evaluated for safety and efficacy assessments at high-dose (2 capsules TID) for 28 days. There will be an evaluation with all safety assessments data to decide whether this study passes the checkpoint to enter Part II.
Diagnosis and Main Criteria:	

Study Population	Patients with ADHD according to the Diagnosis and Statistical Manual of Mental Disorders, 5th Edition
Inclusion Criteria	1. Aged 18-70 years 2. Female subjects of child-bearing potential must test negative to pregnancy and use appropriate birth control method from the beginning of study to the 15 days later after ending of study 3. Subjects must be able to understand and willing to sign informed consent 4. Able to discontinue the use of any psychotropic medications for the treatment of ADHD symptoms at screening 5. Meet strict operational criteria for adult ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) 6. A total score of 20 or higher on the 12-item ADHD index of Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (CAARS-S:S) at screening 7. Have a moderate or severe symptom of ADHD with score of 4 or higher in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) at screening
Exclusion Criteria	1. Have any clinically significant concurrent medical condition (endocrine, renal, respiratory, cardiovascular, hematological, immunological, cerebrovascular, neurological, anorexia, obesity or malignancy) that has become unstable and may interfere with the interpretation of safety and efficacy evaluations 2. Have any clinically significant abnormal laboratory, vital sign, physical examination, or electrocardiogram (ECG) findings at screening that, in the opinion of the investigator, may interfere with the interpretation of safety or efficacy evaluations 3. Have known serological evidence of human immunodeficiency virus (HIV) antibody 4. Are pregnant as confirmed by a positive pregnancy test at screening 5. Have QTc values >450 msec at screening using Fridericia's QTc formula 6. Have current of bipolar and psychotic disorders 7. Have a current major depression disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, panic disorder and eating disorder (also if treated but not currently symptomatic) **NOTE**: Comorbid diagnoses identified during screening and baseline are acceptable provided that ADHD is the primary

	diagnosis and the comorbid diagnoses will not confound study data or impair subject's ability to participate (per the Investigator's judgement and documented in source note). 8. Have any history of a significant suicide attempt, or possess a current risk of attempting suicide, in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). 9. Have a history of jailing or imprisonment in the past 6 months due to worsening of symptoms of ADHD.
Early Withdrawal of Subjects	Subjects will be withdrawn from this trial if they meet one of the following withdrawal criteria: • Subjects wish to withdraw. (Subjects are not obligated to give reasons for discontinuation from this trial.) • Subjects can't obey the regulation of the study. • Investigator considers that withdrawal from study is the best interest of a subject. • The subject is pregnant during the trial. Subjects withdrawn from the study due to adverse event(s) must be followed until the events are recovered, recovered with residual effects, death, or lost to follow-up.
Premature Termination or Suspension of the Study	The Investigator and/or the Sponsor may decide to stop the trial if: • Safety assessment clearly indicates that one study arm is associated with more severe or serious adverse experiences. • The Sponsor decides to terminate the trial if necessary.
Test Product, Dose and Regimen:	
Name	PDC-1421 Capsule
Ingredients	PDC-1421: 380 mg, Silicon dioxide: 10 mg, Magnesium stearate: 10 mg.
Physical Appearance	Yellowish Granules in brownish capsule.
Loss on Drying	NMT 6%
Water Extractives	NLT 80%
Dilute-Alcohol Extractives	NLT 70%
Total Ash	NMT 5%
Acid-Insoluble Ash	NMT 4%
Alcohol Extractives	NLT 38%
TLC	1. One grayish blue band has same R_f value as reference standard (3',6-disinapoylsucrose);

	2. One watchet blue band has same R_f value as reference standard (Glomeratose A).
HPLC of Markers	1. 10.0 mg/g ≤ Glomeratose A ≤ 30.0 mg/g. 2. 38 mg/g ≤ 3',6-Disinapoylsucrose ≤ 95 mg/g.
UV Spectrum	λ_{max}: 230~240 nm; 315~325 nm
IR Spectrum (cm^{-1}, %T)	Peak at: 3380 ± 100 Broad, 2938 ± 20 Sharp, 1605 ± 10 Sharp, 1455 ± 10 Sharp, 833 ± 10 Sharp.
pH	Dissolved in distill deionized water at a concentration of 0.1 g/ml, 3.8 ≤ pH ≤5.8.
Uniformity	90~110%
Weight Variation	90~110%
Heavy Metal	Cu < 20 ppm, As < 1 ppm, Pb < 5 ppm, Cd < 0.2 ppm, Hg < 0.1 ppm
Microbial Purity	Total aerobic plate count: NMT 10^3 CFU/g Mold and yeast count: NMT 100 CFU/g *Echerichia coli*: Undetectable *Staphylococcus aureus*: Undetectable *Salmonella*: Undetectable
Dose and Regimen	1 and 2 capsules thrice daily, p.o., after meal
Clinical Endpoints:	
Primary Endpoint	Improvement of 40% or greater in ADHD Rating Scale-Investigator Rated (ADHD-RS-IV) from baseline up to 8 weeks treatment
Secondary Endpoints	• Change from baseline in the Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (CAARS-S:S) to 8 weeks treatment. • Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) and Clinical Global Impression-ADHD-improvement (CGI-ADHD-I) score of 2 or lower.
Safety Evaluation	A. Change from baseline in: 1. vital sign 2. physical examination 3. electrocardiogram (ECG) 4. laboratory tests (hematology and biochemistry) B. Incidence of AE/SAE C. Suicidal ideation and behavior by Columbia-Suicide Severity Rating Scale (C-SSRS)
Statistical Considerations:	
Sample Size	In part I study, six subjects each will be evaluated for safety and efficacy

Determination	assessments at 1 and then 2 capsules TID dose for total 56 days (28 days at each dose).
General Statistical Methodology	1. Subjects Population • Intent-to-Treat (ITT) Population: The data are analyzed on patients who take at least one dose of study medication and have any post-baseline measurements collected. • Per-protocol (PP) Population: ➢ The drug compliance is at least 80% ➢ Subjects have completed data to determine the primary endpoint. ➢ Subjects cannot have protocol deviation. • Safety Population: The safety measures are conducted on the patients who take at least one dose of study medication. 2. Statistical Method Simple descriptive statistics with 95% confidence interval will be performed with data collected in this study wherever applicable. All data shall be tabulated and presented in the study report. The safety and efficacy data will be analyzed using the non-parametric method wherever appropriate. The purpose for Part I is exploratory in safety and the formal statistical analysis will not be needed. The descriptive statistics will be provided. Safety endpoints will be listed and summarized as appropriate: median and range for continuous data; frequencies, total numbers and percentages for categorical data.

2. Trial Objectives

2.1 Primary Objective

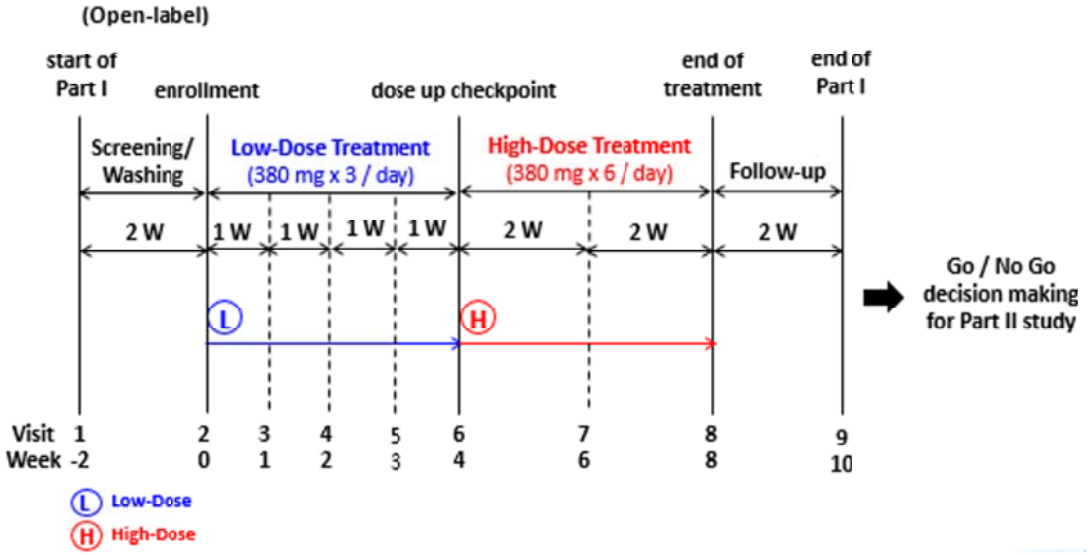
The objective of this trial was to determine the effective doses and treatment period of PDC-1421 Capsule in subjects with ADHD.

2.2 Secondary Objective

The objective was to evaluate the safety of PDC-1421 Capsule in subjects receiving PDC-1421 at various dose levels.

3. 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 targeted population of this Part I study is six subjects who met the intent-to-treat basis. Part I study is an open-label study, single center and dose escalation evaluation in six patients.



Low dose: Six subjects will be initially evaluated for safety and efficacy assessments at low-dose (1 capsule TID) for 28 days. Subject will return for visit once a week during treatment period.

Checkpoint #1: There will be an evaluation with all safety assessments data to decide whether you pass the checkpoint to enter high-dose treatment or continue to receive a low-dose treatment by the investigator.

High dose: The subjects who pass the checkpoint #1 will be initially evaluated for safety and efficacy assessments at high-dose (2 capsules TID) for 28 days. Subject will return for visit biweekly during treatment period.

Checkpoint #2: There will be an evaluation with all safety assessments data to decide whether this study passes the checkpoint to enter Part II by the investigators.

4. Study Endpoints

4.1 Primary Endpoint

Improvement of 40% or greater in ADHD Rating Scale-Investigator Rated (ADHD-RS-IV) from baseline up to 8 weeks treatment.

4.2 Secondary Endpoints

4.2.1 Change from baseline in the Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (CAARS-S:S) up to 8 weeks treatment.

4.2.2 Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) and Clinical Global Impression-ADHD-Improvement (CGI-ADHD-I) score of 2 or lower.

4.3 Safety Evaluation

4.3.1 Change from baseline in:

- vital sign
- physical examination
- electrocardiogram (ECG)
- laboratory tests (hematology and biochemistry)

4.3.2 Incidence of AE/SAE

4.3.3 Suicidal ideation and behavior by Columbia-Suicide Severity Rating Scale (C-SSRS)

5. Randomization and Blinding

	Part I
Randomization	None (open label)
Blinding	None (open label)

6. Treatment of Subjects

6.1 Description of Study Drug

PDC-1421 Capsule is a botanical investigational new drug. Each PDC-1421 Capsule contains 380 mg PDC-1421 drug substance extracted from dry root of *P. tenuifolia*.

6.2 Treatment Schedule

Potential subjects will be introduced by Investigator of the study design at Screening. If the subject agrees to participate and signs the consent form, the screening process will begin. Suitability of the subject will be evaluated by inclusion/exclusion criteria.

In part I Study, six eligible subjects will receive a low-dose treatment with 1 PDC-1421 Capsule thrice daily for 28 days (4 weeks) and be assessed once a week (Visit 2, 3, 4, 5, and 6). After passing a dose-up checkpoint for the safety of individual subjects, these subjects will then receive a high-dose treatment with 2 PDC-1421 Capsules thrice daily for another 28 days (4 weeks). Subjects will be assessed every two weeks (Visit 6, 7 and 8) in high-dose treatment. After the end of part I Study, subjects will be requested to return for a follow-up visit (Visit 9) two weeks later after the last dose.

During the COVID-19 public health emergency, the assessments of CAARS, CGI, ADHDRS, C-SSRS, AE evaluation, Concomitant Medication, Physical examination can be conducted by telephone, video, or email, but those remote assessments should be documented.

Procedure table: BLI-1008-001 protocol									
***Week**	**-2**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
DSM-V	√								
CAARS-S:S	√	√	√	√	√	√	√	√	
CGI-ADHD-S	√	√	√	√	√	√	√	√	
CGI-ADHD-I		√	√	√	√	√	√	√	
ADHD-RS-IV	√	√	√	√	√	√	√	√	
C-SSRS	√	√	√	√	√	√	√	√	√
AE/SAE evaluation			√	√	√	√	√	√	√
Concomitant Medication	√	√	√	√	√	√	√	√	
Physical examination	√							√	
Vital sign	√	√	√	√	√	√	√	√	
ECG	√							√	
Hematology	√	√		√		√	√	√	
Blood Chemistry	√	√		√		√	√	√	
Blood drawing (venipuncture)	√	√		√		√	√	√	
Pregnancy test	√								√

*On ±2 days.

6.2.1 Screening Phase (Visit 1)

The Screening phase will be done within 1~2 weeks period and intended for diagnosing and assessing the patient for possible inclusion in the study and for providing an adequate washout period. The items of physical, rating scales and laboratory examination at screening are outlined below:

- Informed consent
- Subject information, including date of birth, gender, body height and weight
- Medical history (within six month), including any clinically significant psychiatric, neurological, gastrointestinal, renal, hepatic, cardiovascular, respiratory, metabolic, endocrine, hematological or other major disorders
- Pregnancy test
- Physical examination: skin, head, neck, eyes, ears, nose, throat, heart, lungs, abdomen (liver, spleen), neurological examination, lymph node and extremities.

- Vital sign: heart rate, blood pressure, body temperature
- ECG
- Hematology: RBC, WBC, platelets, hematocrit, hemoglobin, prothrombin time (PT), partial thromboplastin time (aPTT)
- Blood chemistry: AST, ALT, LDH, total bilirubin, BUN, serum creatinine, free thyroxine (FT4), TSH, sodium, calcium, potassium, HbA1c, LDL, HDL, triglyceride, cholesterol
- DSM-V, CAARS-S:S , CGI-ADHD-S , ADHD-RS-IV , C-SSRS
- Concomitant medication evaluation
- Eligibility evaluation: laboratory data, other tests and evaluation results shall be obtained at Screening to determine the appropriateness of subject enrolled in this study

6.2.2 Part I Study. - Treatment Period (Visit 2~8) and Follow-up (Visit 9)

Subjects who meet the eligibility criteria will be enrolled and take test drug at this period. Six eligible subjects will take 1 capsule of PDC-1421 Capsule thrice daily for four weeks. They will receive a drug bag and be instructed to take 1 PDC-1421 Capsule thrice daily after meals. Weekly visits (Visit 2, 3, 4 and 5) will be requested during this 28-day treatment period. At Visit 6, all subjects will be evaluated with safety assessments and to be decided whether they will enter the high-dose treatment by the investigator. In the high-dose treatment, subjects will receive a drug bag and be instructed to take 2 PDC-1421 Capsule thrice daily after meals for 4 weeks. Biweekly visits (Visit 6, 7 and 8) will be requested during this 28-day treatment period. After two weeks of the last dose administration, subjects are assessed for a follow-up. Then, a checkpoint will be conducted. If subjects have no drug-related SAE, the schedule can be conducted to the part II. The items of safety and efficacy parameters at treatment period are outlined below:

- Physical examination: skin, head, neck, eyes, ears, nose, throat, heart, lungs, abdomen (liver, spleen), neurological examination, lymph node and extremities (only at Visit 8).
- Vital sign: heart rate, blood pressure, body temperature
- ECG (Only at Visit 8).
- Hematology: RBC, WBC, platelets, hematocrit, hemoglobin, prothrombin time (PT), partial thromboplastin time (aPTT) (Only at Visit 2,4,6,7 and 8).
- Blood chemistry: AST, ALT, LDH, total bilirubin, BUN, serum creatinine, free thyroxine (FT4), TSH, sodium, calcium, potassium, LDL, HDL, triglyceride, cholesterol (Only at Visit 2,4,6,7, and 8).
- CAARS-S:S, CGI-ADHD-S, CGI-ADHD-I, ADHD-RS-IV, C-SSRS and concomitant medication evaluation.
- AE/SAE evaluation (Subjects will not need to be assessed for AE/SAE at visit 2.)
- Drug accountability

Follow-up visit will be performed at visit 9 after two weeks of the last dose administration. The test items are outlined in the following:

- C-SSRS.
- AE/SAE evaluation
- Pregnancy test

6.3 Other Medication During the Study

To avoid conflict or unknown effects with the study drug, subjects are prohibited from taking any anti-ADHD medication and psychoactive drugs, as per the exclusion criteria, including MAOIs (monoamine oxidase inhibitor), NRIs (norepinephrine reuptake inhibitor) and norepinephrine receptor agonist/antagonist. Subjects can't combine the newly-initiated psychotherapy. If subjects have severe insomnia and are currently taking Zolpidem, Zopiclone or Zaleplon (sedative-hypnotics), they will be queried whether they can comply with the discontinuation:

- Subjects who indicate that they can discontinue will be washed out for 1 week, and then allowed to begin study protocol;
- Subjects who indicate that they are unable to discontinue will be allowed to enroll if they are able to agree that their use will be consistent and will not change for the duration of the study. (The maximum daily dose in Zolpidem, Zopiclone and Zaleplon are 10 mg, 7.5 mg and 10 mg respectively.)

7. Protocol Versions and Protocol Amendments

Approved versions of study protocol are listed as following.

Version No.	Version Date
Version 1.2	2018/06/06
Version 1.6	2019/03/22
Version 1.7	2019/05/03
Version 1.8	2019/07/26
Version 1.9	2020/01/15
Version 2.0	2020/06/30

Amendments relevant to statistical parts from version 1.2 to 2.0 are highlighted / crossed-out in table below:

Summary of statistical changes for protocol version 1.6
8.3 Analysis of Efficacy and Safety The statement "The comparison between three groups will be analyzed by nonparametric method as appropriate" was revised to "The comparison between two groups will be analyzed by nonparametric method as appropriate".
Summary of statistical changes for protocol version 1.7
No amendments on statistical parts.
Summary of statistical changes for protocol version 1.8

No amendments on statistical parts.

Summary of statistical changes for protocol version 1.9

8.2 Statistical Method

The first paragraph was revised to "Simple descriptive statistics with 95% confidence interval will be performed with data collected in this study wherever applicable. All data shall be tabulated and presented in the study report. The safety and efficacy data will be analyzed using the non-parametric method wherever appropriate."

8.3 Analysis of Efficacy and Safety

- The third item of definition of protocol deviation was deleted.
- The definition of an intent-to-treat (ITT) basis was revised to "the data are analyzed on patients who take at least one dose of study medication and have any post-baseline measurements collected."
- The statement "The safety measures are conducted on the ITT basis" was revised to "The safety measures are conducted on the patients who take at least one dose of study medication."
- The statement "The comparison between two groups will be analyzed by nonparametric method as appropriate" was deleted.

Summary of statistical changes for protocol version 2.0

3.1 General Design

The statement "The targeted population of this Part I study is six subjects who met the per-protocol basis" was revised to "The targeted population of this Part I study is six subjects who met the intent-to-treat basis."

8. Timing and Operating Procedures for Final Analysis

The final analysis will be planned according to the study protocol. The timing of analysis and data to be cleaned is detailed as following:

(1) Data to be cleaned: When 6 subjects have been recruited and all subjects are off study. All clinical trial data will be cleaned up for the analyses.

(2) Timing of analysis: After all clinical trial data were cleaned up and the database will be locked for the final analysis. Then, all data will be analyzed according to SAP. Statistical programs will be prepared and executed by NHRI.

9. Definitions

9.1 Age (years)

(Date of informed consent form signed–Date of Birth+1) / 365.25. Round down to an integer.

9.2 Treatment Compliance (%)

Subjects' compliance during the treatment period will be calculated according to the following formula:

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

= (Number of study medication should be taken per day) * (Extent of exposure).

Number of study medication actually took = quantity of dispensed capsules – quantity of returned capsules – quantity of lost capsules.

- Extent of exposure (days):

  Extent of exposure before Checkpoint 1 = date of V6 – date of the first drug taken.

  Extent of exposure after Checkpoint 1 = date of the last drug taken – date of V6 + 1.

Subjects' mean daily dose of the test drug will be calculated by

$$\frac{\text{Number of study medication actually took}}{\text{Extent of exposure}}$$

- If the date of the 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.

9.3 ADHD-RS-IV

The ADHD-RS-IV with Adult Prompts is an 18-item scale base on the DSM-IV-TR' criteria for ADHD that provides a rating of the severity of symptoms. The adult prompts serve a guide to explore more fully the extent and severity of ADHD symptoms and create a framework to ascertain impairment. The odd-numbered 9 items assess inattentive symptoms and the even-numbered 9 items assess hyperactive-impulsive symptoms. Scoring is based on a 4-point, yielding a possible total score of 0~54. Likert-type severity scale: 0 = Never or Rarely, 1 = Sometimes, 2 = Often, 3 = Very Often. Clinicians should score the highest score that is generated for the prompts for each item.

For inattention (IA) subscale raw score: Add the odd-numbered 9 items

For hyperactivity-impulsivity (HI) subscale raw score: Add the even-numbered 9 items

To obtain the total raw score: Add the IA and HI subscale raw scores.

9.4 Clinical Global Impression

At the baseline visit, clinicians completed the CGI-S and were asked to evaluate the severity of subjects' illness with respect to ADHD symptoms based on the clinician's experience with this particular population. Possible scores ranged from 1 (normal, not ill at all) to 7 (among the most extremely ill subjects). At all subsequent study visits, clinicians used the CGI-I to rate the subjects' total improvement based on comparison with their baseline assessment from 1 (very much improved) to 7 (very much worse).

9.5 CAARS-S:S

Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (Conners et al., 1998; CAARS-S:S) consists of 26 items rated from 0 'not at all, never' to 3 'very much, very frequently.' Four subscales each composed of 5 items (A: Inattention/Memory Problems; B: Hyperactivity/Restlessness; C: Impulsivity/Emotional Lability; and D: Problems with Self-Concept) as well as a 12-item ADHD index can be computed. The CAARS-S:S was administered by computer-assisted personal interview (CAPI) prior to the first treatment session.

9.6 C-SSRS

9.6.1 Suicidal Ideation

The five boxes in the Suicidal Ideation, from the left to the right, of the CRF represents the five binary responses (yes/no) of the five items are as following.

1. Wish to be Dead (C1)
2. Non-Specific Active Suicidal Thoughts (C2)
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act (C3)
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan (C4)
5. Active Suicidal Ideation with Specific Plan and Intent (C5)

9.6.2 Intensity of Ideation

The first box of the six boxes in the Intensity of Ideation of the CRF records the most severe type of suicidal ideation. The remaining boxes, from the left to the right, represent the following items.

#1. Frequency

(1 = Less than once a week, 2 = Once a week, 3 = 2-5 times in week, 4 = Daily or almost daily, 5 = Many times each day)

#2. Duration

(1 = Fleeting – few seconds or minutes, 2 = Less than 1 hour/some of the time, 3 = 1-4 hours/a lot of time, 4 = 4-8 hours/most of day, 5 = More than 8 hours/persistent or continuous)

#3. Controllability

(1 = Easily able to control thoughts, 2 = Can control thoughts with little difficulty, 3 = Can control thoughts with some difficulty, 4 = Can control thoughts with a lot of difficulty, 5 = Unable to control thoughts, 0 = Does not attempt to control thoughts)

#4. Deterrents

(1 = Deterrents definitely stopped you from attempting suicide, 2 = Deterrents probably stopped you, 3 = Uncertain that deterrents stopped you, 4 = Deterrents most likely did not stop you, 5 = Deterrents definitely did not stop you, 0 = Does not apply)

#5. Reasons for Ideation

(1 = Completely to get attention, revenge or a reaction from others, 2 = Mostly to get attention, revenge or a reaction from others, 3 = Equally to get attention, revenge or a reaction from others and to end/stop the pain, 4 = Mostly to end or stop the pain, 5 = Completely to end or stop the pain, 0 = Does not apply)

9.6.3 Suicidal Behavior

The boxes in the Suicidal Behavior, from the left to the right, of the CRF represents the binary responses (yes/no) of the items are as following.

6. Actual Attempt (C9)
7. Non-Suicidal Self-Injurious Behavior (Self-injurious behavior without suicidal

intent)

8. Interrupted Attempt (C8)
9. Aborted Attempt (C7)
10. Preparatory Acts or Behavior (C6)
11. Suicidal Behavior
12. Completed Suicide (C10, not available in screening)

10. Statistical Methodology

10.1 Analyzed Populations

10.1.1 Intent-to-Treat (ITT) Population

The data are analyzed on patients who take at least one dose of study medication and have any post-baseline measurements collected.

10.1.2 Per-protocol (PP) Population

- The drug compliance is at least 80%.
- Subjects have completed data to determine the primary endpoint.
- Subjects cannot have protocol deviation.

10.1.3 Safety Population

The safety measures are conducted on the patients who take at least one dose of study medication.

10.2 Sample Size Determination

In part I study, six subjects each will be evaluated for safety and efficacy assessments at 1 and then 2 capsules TID dose for total 56 days (28 days at each dose).

10.3 Data Handling

10.3.1 Definition of Baseline Values

The data obtained from eligible subjects before study drug administration in Visit 2 are set as baseline.

10.3.2 Data Handling for Missing Data

The data are analyzed utilizing the last observation carried forward (LOCF) technique to impute the missing data.

10.3.3 Definition of Protocol Deviation

- Inclusion or exclusion criteria not satisfied.
- Not permitted concomitant medications.

10.4 General Statistical Methodology

The purpose for Part I is exploratory in safety and the formal statistical analysis will not be needed. All data shall be tabulated and presented in the study report. The descriptive statistics will be provided. 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. 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. Simple descriptive statistics with 95% confidence interval will be performed with data collected in this study wherever applicable. The safety and efficacy data will be analyzed using the non-parametric method wherever appropriate.

10.5 Disposition of Subjects

- Entered subject number
- Overall status and reason of withdraw / early termination

10.6 Demographic and Baseline Characteristics

10.6.1 Demographic Characteristics

- Age
- Gender
- Height (cm)
- Weight (lb)

10.6.2 Baseline Characteristics

- DSM-V (score)
  - Inattention Symptoms
  - Hyperactivity Symptoms
  - Impulsivity Symptoms
- ADHD-RS-IV (score)
  - Inattention Subscale
  - Hyperactivity-Impulsivity Subscale
  - Total Score
- CAARS-S:S (score)
  - Inattention/Memory Problems
  - Hyperactivity/Restlessness
  - Impulsivity/Emotional Lability
  - Problems with Self-Concept
  - ADHD index
- Clinical Global Impression (score)
  - Severity of illness
  - Improvement
- Physical Examinations
  - Skin
  - Head and Neck
  - Eyes
  - Ears
  - Nose
  - Throat
  - Heart
  - Lungs
  - Abdomen / liver, spleen

  - Extremities
  - Neurological
  - Lymph Node
- Vital Signs
  - Systolic Blood Pressure (mm/Hg)
  - Diastolic Blood Pressure (mm/Hg)
  - Heart Rate (bpm)
  - Temperature (°F)
- Electrocardiogram (ECG)
  - QTc value (msec)
- Hematology
  - RBC (g/dL)
  - WBC ($x10^3/mm^3$)
  - Hemoglobin (g/dL)
  - Hematocrit (%)
  - Platelet ($x10^3/mm^3$)
  - aPTT (sec)
  - PT (INR)
- Biochemistry
  - BUN (mg/dl)
  - Creatinine (mg/dl)
  - Total Bilirubin (mg/dl)
  - Sodium (mmol/L) (Na)
  - Calcium (mmol/L) (Ca)
  - Potassium (mmol/L) (K)
  - AST (U/L) (SGOT)
  - ALT (U/L) (SGPT)
  - LDH (U/L)
  - TSH (mui/ml)
  - Free T (ng/dl)
  - HbA1c (%)
  - LDL (mg/dL)
  - HDL (mg/dL)
  - Triglyceride (mg/dL)
  - Cholesterol (mg/dL)
  - HCG (Pregnancy Test)
- C-SSRS
  - Suicidal Ideation
  - Suicidal Behavior

10.7 Efficacy Analyses

In part I study, efficacy assessments are conducted from screening stage to the last visit. Efficacy parameters are outlined as follows:

- ADHD-RS-IV
- Clinical Global Impression
- CAARS-S:S

10.7.1 Primary Efficacy Analyses

- The scores of ADHD-RS-IV will be assessed by the descriptive statistics of tendency and variability.
- The improvement, which is greater than or equal to 40%, in ADHD-RS-IV from baseline up to 8 weeks (V3~V8) treatment will be summarized by way of frequency and percentage.

10.7.2 Secondary Efficacy Analyses

- The *T*-scores of CAARS-S:S (Conners et al. 1999) will be assessed for each visit change from baseline (V3-V2, V4-V2,…,V8-V2) by Wilcoxon signed-rank test.
- The scores of 2 or lower of CGI-ADHD-S (V1~V8) and CGI-ADHD-I (V3~V8) will be summarized by way of frequency and percentage.

10.8 Safety Analyses

Safety parameters are outlined as follows:

- Data collected from the physical examinations, vital sign, ECG and laboratory test in scheduled visit
- Adverse events reported
- Serious adverse events reported
- C-SSRS evaluation

The data obtained before study drug administration in Visit 2 are set as baseline. After the beginning of treatment, the collection of data of safety parameters are performed at planned treatment schedule as section 6.2. AE or SAE will be closely monitored during the study period. CRC shall record these data in CRF in detail. In part I, data are recorded from screening stage to the last visit.

10.8.1 Adverse Event (AE)

Adverse event is any unfavorable and unintended symptom, syndrome, medical condition or experience that develops or worsens within the study period. In this Phase II trial, any clinically significant abnormal findings, including causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, are considered to be AEs and will be monitored and recorded. AE may not be causal relationship with study medication or clinical study. Whether related to study medication or not, CRC shall record the information of AEs in CRF. The information of AEs contains characteristic, onset and duration, frequency, the Investigator's opinion of the relationship to the study drug (unrelated, unlikely, possibly, probably, definitely), outcome (recovered,

recovered with residual effects, continuing, death, lost to follow-up) and severity. Common Terminology Criteria for Adverse Events v4.03 (CTCAE) is a descriptive terminology and the grading (severity) scale is provided for each AE term. In the final analysis, all adverse events will be summarized with coding term, severity, relationship to study drug by frequency tables with the counts and percentage.

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.8.2 Serious Adverse Event (SAE)

SAE is defined as any significantly untoward medical occurrence, including:

- Death
- Life-threatening condition
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment/damage

10.8.3 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

SUSAR is defined as any significantly untoward medical occurrence, the nature or severity of:

- Which is not consistent with the applicable product information (e.g., Investigator's Brochure) for an unapproved investigational medicinal product.
- Which must be causal relationship with study medication or clinical study

10.8.4 Other Safety Endpoints

- Physical examinations will be summarized for V8 change from V1 by way of frequency and percentage.
- Vital signs will be summarized for each treatment visit (V3~V8) change from baseline by way of frequency and percentage, and assessed by the descriptive statistics of tendency and variability.
- The ECG will be summarized for V8 change from V1 by way of frequency and percentage, and assessed by the descriptive statistics of tendency and variability.

- Hematology will be summarized for some visits (V4, V6, V7, V8) change from baseline by way of frequency and percentage, and assessed by the descriptive statistics of tendency and variability.
- Biochemistry will be summarized for some visits (V4, V6, V7, V8) change from baseline by way of frequency and percentage except for HbA1c, and assessed by the descriptive statistics of tendency and variability. The HCG (pregnancy test) will be summarized for V9 change from V1 by way of frequency and percentage.
- C-SSRS (Nilsson et al. 2013)
  - Suicidal Ideation (C1~C5), Suicidal Behavior (C6~C10), and Self-Injurious Behavior without Suicidal Intent will be summarized for each visit (V1~V9) by way of frequency and percentage.
  - Some Suicide-Related Treatment-Emergent Events will be summarized by way of frequency and percentage.
  - Categories (C1~C10) will be summarized by a shift-table to demonstrate changes some visits (V3~V8) from baseline.
  - The most severe type of suicidal ideation will be summarized by a shift-table to demonstrate changes some visits (V3~V8) from baseline. We define no suicidal ideation as 0.

11. Programming Considerations

11.1 Statistical Software and Format of Output

Results presented in tables, figures and graphs (section 14 of ICH/CSR) and in patient data listing (section 16 of ICH/CSR) will be created with SAS version 9.4 or above. The format (mock-up table/figure and listing) can be found in Appendix.

11.2 SAS Procedures for Descriptive/Inferential Statistics

Statistics	Relevant Syntax
Descriptive Statistics For Categorical Variable	**PROC FREQ** DATA = aaa; TABLES variable; **RUN**;
Descriptive Statistics For Continuous Variable	**PROC MEANS** DATA = bbb N MEAN STD MIN MEDIAN MAX LCLM UCLM ALPHA=**0.05**; VAR variable; **RUN**;
Wilcoxon signed-rank test	**PROC UNIVARIATE** DATA = ccc; VAR variable; **RUN**;

12. Reference

- A Phase II Tolerability and Efficacy Study of PDC-1421 Treatment in Adult Patients with Attention-Deficit Hyperactivity Disorder (ADHD), Part I (Protocol Number: BLI-1008-001)

- Conners, C. K., Erhardt, D., & Sparrow, E. P. (1999). Conners' adult ADHD rating scales (CAARS): technical manual. North Tonawanda, NY: Multi-Health Systems.
- Nilsson, M. E., Suryawanshi, S., Gassmann-Mayer, C., Dubrava, S., McSorley, P., & Jiang, K. (2013). Columbia–suicide severity rating scale scoring and data analysis guide. CSSRS Scoring Version, 2, 1-13.

13. Appendix

13.1 Normal Range of Laboratory Tests

Clinical Laboratories, Department of Laboratory Medicine, the Medical Center at the University of California, San Francisco, CA 94143.

- 2019-08-15
- 2020-02-01

13.2 Mock-up Tables

13.3 Mock-up Patient Data Listings