BioLite, Inc.
萊特先進生醫股份有限公司

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PROTOCOL

Investigational New Drug (IND)

PDC-1421 Capsule

(*Polygala tenuifolia* Willd.)

EDITION NUMBER : Version 1.7
SPONSOR : BioLite, Inc.
American BriVision Corporation
RELEASE DATE : 2022/08/29

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

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PROTOCOL SYNOPSIS

Name of sponsor	BioLite, Inc. / American BriVision Corporation
Name of finished product	PDC-1421 Capsule
Name of active ingredient	PDC-1421
Protocol title	A Phase II Tolerability and Efficacy Study of PDC-1421 Treatment in Adult Patients with Attention-Deficit Hyperactivity Disorder (ADHD), Part II
Clinical trial phase	Phase II
Study site	Multiple sites
Study period	2 years
Study population	Patients with ADHD according to the Diagnosis and Statistical Manual of Mental Disorders, 5th Edition
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.
Study design	Randomized, double-blind, placebo-controlled, parallel groups
Sample size	Maximum 99 subjects
Test product	PDC-1421 Capsule
Dose and regimen	1 and 2 capsules thrice daily, p.o., after meal
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 II is a randomized, double-blind, placebo-controlled, parallel-group study. At first stage, a number of 69 subjects will be randomly assigned on a 1:1:1 basis to one of the three arms (1 PDC-1421 Capsule plus 1 placebo TID, 2 PDC-1421 Capsules TID, 2 placebo TID) for 8 weeks and evaluated the safety and efficacy every two weeks during the treatment period. An interim analysis will be conducted to evaluate the efficacy of PDC-1421 and to decide whether

	it is necessary enter the second stage of Part II study in which 30 subjects will be randomly assigned on a 1:1:1 basis to one of the three treatment arms and receive the same treatment.
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	• Symptom remission in ADHD Rating Scale-Investigator Rated (ADHD-RS-IV total score ≤ 18) up to 8 weeks treatment. • Change from baseline in the ADHD Rating Scale-Investigator Rated (ADHD-RS-IV), Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (CAARS-S:S) and Empirical-Sluggish Cognitive Tempo (E-SCT) score up to 8 weeks treatment. • Clinical Global Impression - improvement (CGI-I) score of 2 or lower up to 8 weeks treatment.
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 method	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. The primary endpoint will be analyzed by chi-square test, while the secondary endpoints will be analyzed using the ANOVA or Kruskal-Wallis non-parametric ANOVA test for continuous endpoints and chi-square test for binary endpoints.

LIST OF ABBREVIATIONS/DEFINITIONS

- ADHD
  Attention-Deficit/Hyperactivity Disorder
- ADHD-RS-IV
  Attention-Deficit/Hyperactivity Disorder Rating Scale-IV
- AE
  Adverse Events, whether or not considered related to the investigational drug, must be recorded in CRF.
- CAARS-S:S
  Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version
- CGI-I
  Clinical Global Impression- Improvement
- CGI-S
  Clinical Global Impression- Severity
- CHO
  Chinese Hamster Ovary
- Clinical monitor
  The designated CRA monitoring this study for the sponsor
- CRA
  Clinical Research Associate
- CRC
  Clinical Research Coordinator
- CRF
  Case Report Form
- CRO
  Contract Research Organization
- C-SSRS
  Columbia-Suicide Severity Rating Scale
- DLT
  Dose limiting toxicities
- DSM-5
  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.
- HDL
  High-Density Lipoprotein
- HED
  Human Equivalent Dose
- HPLC
  High Performance Liquid Chromatography
- ICF
  Informed Consent Form
- ICH-GCP
  International Conference of Harmonization-Good Clinical Practice
- IEC
  Independent Ethics Committee
- IRB
  Institutional Review Board
- LDH
  Lactate Dehydrogenase
- E-SCT
  Empirical-Sluggish Cognitive Tempo
- LDL
  Lower-Density Lipoprotein
- NET
  Norepinephrine Transporter
- NLT
  Not Less Than
- NMT
  Not More Than
- NOAEL
  No Observable Adverse Effect Level
- NRI
  Norepinephrine Reuptake Inhibitor
- PITDC

Medical and Pharmaceutical Industry Technology and Development Center

- SAEs

  Serious Adverse Event(s), whether or not considered as related to the investigational drug must be recorded and reported.

  The serious adverse event is defined as following:

  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

- Severity Rating of AE

  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.

- SHR

  Spontaneous hypertensive rat

- SOP

  Standard Operation Procedure

- 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.

- TID

  Three times a day

- WKY rat

Wistar-Kyoto rat

- TLC
  Thin Layer Chromatography

1. Background Information

1.1 Description of PDC-1421 Capsule

PDC-1421 Capsule is a botanical investigational new drug containing the extract of Radix Polygalae (*Polygala tenuifolia* Willd.) as active ingredient. Radix Polygalae is a traditional herb commonly prescribed in China to induce sedation, benefit the mentality and to promote expectoration. It has also been used for insomnia, anxiety, and heart palpitations[1].

1.1.1 Preparation

Raw materials originated from *P. tenuifolia* were obtained from Shanxi, China. After having been cleaned, and residual stems removed, the root was sun-dried and become the botanical raw material for producing the study drug (PDC-1421 capsule). Raw materials shall comply with physical/chemical specifications, and fingerprint determination via HPLC and TLC shall show desired contents. The materials shall comply criteria for heavy metal, pesticide residues and aflatoxins to avoid contaminations. Acceptable raw materials were water extracted, partially purified by column chromatography, concentrated, and spray-dried to become the drug substance PDC-1421, a yellowish powder. The yield rate from raw materials to PDC-1421 is about 1.4%. Formulation and encapsulation of drug substance PDC-1421 produced the final product of PDC-1421 Capsule. Specifications of PDC-1421 Capsule are tabulated in Table 1.

Table 1. Specifications of PDC-1421 Capsule

Test Items	Specifications
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

NMT: not more than; NLT: not less than

PDC-1421 used in phase I clinical trial was manufactured at the Medical and Pharmaceutical Industry Technology and Development Center (PITDC) in New Taipei City, Taiwan. In order to scale up the production and in compliant with GMP (Good Manufacturing Procedures), the producer has been changed to the Herbal Medicine GMP Plant of the Industrial Technology Research Institute (ITRI) in Hsinchu County, Taiwan. Products produced at ITRI Plant have been tested and meet defined specifications prior to be used in this study.

1.1.2 Composition

Each PDC-1421 Capsule consists of 380 mg PDC-1421 drug substance and 20 mg of excipients. The composition of PDC-1421 Capsule is shown in Table 2.

Table 2. Composition of PDC-1421 Capsule

Name of Ingredient	mg per Capsule	Function
PDC-1421	380 mg	Active ingredient
Silicon dioxide	10 mg	Excipient
Magnesium stearate	10 mg	Excipient

1.1.3 Storage and Handling

During stability test, physical examination, loss on drying and contents assays of the characteristic markers (3',6-disinapoylsucrose and Glomeratose A) were conducted. The results indicated that PDC-1421 Capsule is stable when stored in a well-closed brown bottle at room temperature for at least 36 months.

1.2 Non-clinical Study of PDC-1421

Pharmacology studies were conducted at MDS Pharma Services, Taiwan. Non-clinical toxicity studies were conducted in accordance with Good Laboratory Practice at the Development Center for Biotechnology, Taiwan. Safety pharmacology studies were compliance with Good Laboratory Practice by Level Biotechnology, Inc. and Charles River Laboratory, Inc. Pharmacodynamics studies were conducted at PITDC, Taiwan.

1.2.1 Efficacy Pharmacology

Two *in vitro* studies and one *in vivo* study have been completed to evaluate pharmacological activities of PDC-1421.

1.2.1.1 Radio-ligand Binding Assay

Radio-ligand binding assays were performed on 168 molecular targets, including receptors, ion channels and transporters, to discover the possible functional agonism and/or antagonism of PDC-1421 at concentration of 100 μg/ml. Table 3 showed the result in this study, indicating that PDC-1421 specifically inhibited norepinephrine transporter. Other molecules, such as histamine receptor or cholinergic receptor, were not significantly influenced. The results suggested that PDC-1421 shall not induce side effects such as hypersomnia or dry month. Subsequent studies applying different concentration showed that the inhibition of norepinephrine transporter by PDC-1421 is dose-dependent, within 3 to 100 μg/ml. Norepinephrine transporter inhibitors have developed as the ADHD treatment, such as Atomoxetine. Therefore, PDC-1421 has the potential to be used as an ADHD medication. The subsequent studies were performed to investigate the activities of PDC-1421 used to treat ADHD.

Table 3. Summary of Significant Activities in radio-ligand binding assay

Assay Name	IC_{50} (μg/ml)
Norepinephrine Transporter (NET) Binding	11.8

1.2.1.2 Neurotransmitter Uptake Assay

Atomoxetine, which is one of ADHD medications on market is a potent norepinephrine uptake inhibitor *in vitro* and *in vivo* with relatively low affinity for serotonin and dopamine uptake processes[2,3]. Uptake assays were conducted to study the effect of PDC-1421 on the reuptake of norepinephrine, serotonin and dopamine. The results of uptake assay are summarized in Table 4.

Table 4. Summary for neurotransmitter uptake assay

Assay Name	Test Substance	Dose	Inhibition %	IC_{50}
Norepinephrine Uptake	PDC-1421	1 μg/mL	52	0.70 μg/mL
	Desipramine			0.44 μg/mL (1.66 nM)
Dopamine Uptake	PDC-1421	300 μg/mL	55	246 μg/mL
	Nomifensine			1.62 μg/mL (6.83 nM)
Serotonin Uptake	PDC-1421	100 μg/mL	52	107 μg/mL
	Fluoxetine			0.87 μg/mL (2.83 nM)

PDC-1421 inhibited Norepinephrine reuptake at a 0.70 μg/mL, much lower than of the concentration to inhibit dopamine (246 μg/mL) or serotonin (107 μg/mL). The results indicated that primary pharmacological effect of PDC-1421 may be with its norepinephrine reuptake inhibition, rather than serotonin or dopamine reuptake inhibition. The results are consistent with radio-ligand binding assay, indicated that PDC-1421 is highly specific in the inhibition of norepinephrine transporter.

1.2.1.3 Tetrabenazine (TBZ)-induced Hypothermia Model

According to above assays, PDC-1421 is a selective norepinephrine reuptake inhibitor. A previous study has shown that the elevated concentration of norepinephrine produced by norepinephrine reuptake inhibitor (NRI) resulted in elevation of body temperature in reserpine-induced hypothermia animal model[4]. Reversed temperature in hypothermia model is an index to quantify the effect of NRI.

PDC-1421 was tested by the TBZ-induced hypothermia model to study the effect on norepinephrine reuptake inhibition. Vehicle, PDC-1421 and imipramine (positive control) were orally administrated to individual groups of experimental mice one hour before TBZ treatment and body temperatures were recorded at appropriate time point. The results were summarized in Table 5.

Table 5. Summary for pharmacology study on norepinephrine reuptake inhibition.

Treatment	Dose (mg/kg)	% Inhibition in Body Temperature		
		60 min after TBZ	90 min after TBZ	120 min after TBZ
PDC-1421	10	5	0	0
PDC-1421	30	30	33	27
PDC-1421	100	55*	59*	63*
PDC-1421	300	77*	74*	80*
Imipramine	3	89*	84*	83*

* The inhibition of TBZ-induced hypothermic response by ≧50% is considered as significant response

The results suggest that PDC-1421 at 100 mg/kg p.o. may be associated with NRI activity as evidenced by effect on TBZ-induced hypothermia in mice.

1.2.1.4 Spontaneous hypertensive rat (SHR) Model

According to above assays, PDC-1421 is a selective norepinephrine reuptake inhibitor. Norepinephrine has also been proposed to play a key role in the pathophysiology and pharmacotherapy of ADHD[5,6,7]. The SHR is a valid and currently accepted model for the study of ADHD[9]. The SHRs are known to display hyperactivity, impulsivity, poor sustained attention, and deficits in learning and memory processes in comparison with normotensive Wistar-Kyoto (WKY) rats[10]. In order to proof of concept that PDC-1421 possess the potential of treating ADHD, a local motor activity assay was performed by using SHR. Horizontal activity of SHR is recorded within one hour in Automated Locomotor Activity Analysis System Chamber. Intraperitoneal injection of 5 mg/kg atomoxetine, as a positive control, inhibited total activity of SHR rats significantly after 1 and 4 days administration. Atomoxetine is oral capsule in treatment usage. The course of treatment of atomoxetine need one to three weeks for a good therapeutic response. The absorption of intraperitoneal injection is better than oral administration. PDC-1421 designed as an oral drug substance. To determent PDC-1421 anti-ADHD effective dose, SHR, males, were orally given PDC-1421 dissolved in Saline at a dosage of 75, 225 or 675 mg/kg bodyweight at each exposure. The data revealed that oral administration of PDC-1421 for 4 days significantly inhibit total activity of SHR rats at the concentration of 675 mg/kg.

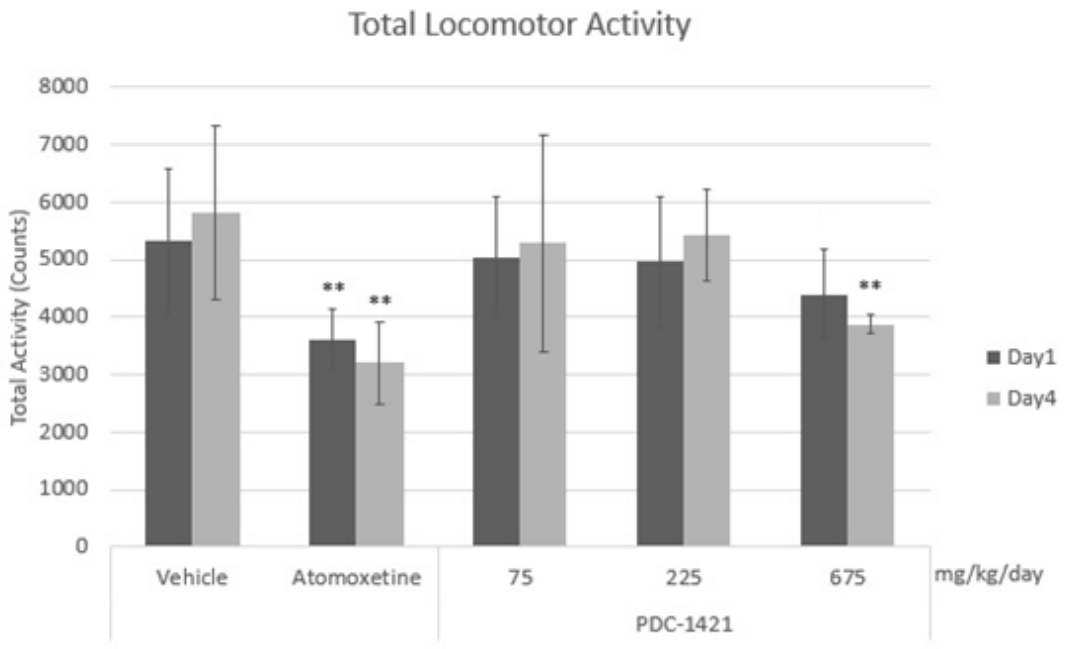


Figure 1. The local motor activity assay in different dose of PDC-1421.
Double-asterisk (**) represents P-value <0.01 between control and treatment groups.

1.2.2 Safety Pharmacology

In order to verify the possible adverse reactions , five studies were conducted to evaluate the effects of PDC-1421 on central nervous system, autonomic system, cardiovascular function, respiratory function, gastrointestinal system, renal function, allergy, inflammation, metabolism and hERG tail current assay:

- EfficacyProfiling *in vivo*®
- Safety Pharmacology Testing Package
- AdverseEventProfiling *in vivo*®
- Safety Pharmacology test in Central Nervous System, Cardiovascular System and Respiratory System
- hERG tail current assay

The significant findings were summarized in Table 6.

Table 6. Summary of the finding in safety pharmacology

Study package	**Study condition and findings**
Efficacy Profiling	• Oral administration of PDC-1421 at 3000 mg/kg did not cause any significant change *in vivo* studies. • PDC-1421 at 300 μg/ml did not demonstrate any significant activity (≧50% change) *in vitro* studies.
Safety Pharmacology Testing Package	PDC-1421 concentration at 300 μg/mL: • Decrease in acetylcholine and $BaCl_2$-induced constriction in guinea pig ileum.
Adverse Event Profiling *in vivo*®	PDC-1421 oral dose at 3000 mg/kg: • Inhibition of gastric emptying in fasted rats (-45%) PDC-1421 oral dose at 3000 mg/kg for 7 days: • Increase in RBC on day 2 in blood chemistry • Increase in K^+ and decrease in glucose on day 2 in blood chemistry • Decrease in LDH (lactate dehydrogenase) on day 8 in blood chemistry
Safety Pharmacology test in Cardiovascular System	• RR interval elongation, heart rate decrease, diastolic arterial pressure decrease and increased sinoatrial arrest incidence were found in dogs in 2500 mg/kg group. • Diastolic arterial pressure decrease was found in dogs in 2500 mg/kg group.
hERG tail current assay	Below the dosage, 0.8 mg/ml PDC-1421, should be viewed as the “no effect concentration” in this assay.

Few effects, including gastrointestinal effects, electrolytes equilibrium, blood sugar value, heart rate decrease and diastolic arterial pressure decrease were found in safety pharmacology. These findings provided scientific evidence in further clinical study to evaluate the influence of PDC-1421.

1.2.3 Cytochrome P450 Interaction with PDC-1421

Cytochrome P450 (CYP450) enzyme assay was conducted for PDC-1421 to evaluate existence of potential drug interaction. The IC_{50} values of each CYP450 isozymes are summarized in Table 7.

Table 7. Summary of IC_{50} values of CYP450 isozymes

CYP isozyme	Species	Concentration	Inhibition %	IC_{50}
CYP 1A2	Human	100 μg/mL	54	84 μg/mL
CYP 2C9	Human	100 μg/mL	57	74 μg/mL
CYP 2C19	Human	100 μg/mL	67	51 μg/mL
CYP 2D6	Human	100 μg/mL	69	53 μg/mL
CYP 3A4	Human	100 μg/mL	58	67 μg/mL

A lower potential of causing drug-drug interaction was verified with lower CYP450 inhibition in this study. IC_{50} of CYP inhibition is higher than IC_{50} of *in vitro* pharmacological study (11.8 and 0.7 μg/mL in NET radioligand binding assay and reuptake assay, respectively), indicating that taking PDC-1421 with substrate of these CYP enzymes, including imipramine, paroxetine and warfarin, may not influence the blood concentration of these prescribed drugs.

1.2.4 Toxicology

Toxic effects of investigational drug are important considerations for human use. Several toxicology studies have been conducted to evaluate the toxic effects of PDC-1421.

1.2.4.1 Single Dose Acute Toxicity Study in Rats

Acute toxicity of test drug may predict effect of over dose. Four doses of PDC-1421 at 0, 1250, 2500 and 5000 mg/kg p.o. were given to different groups of rats. General demeanor, clinical signs, mortality, body weight and gross necropsy findings were evaluated and recorded. There has been no treatment-related pharmacological effect found with all 4 doses. Therefore, the “no observable adverse effect level” (NOAEL) is set at 5000 mg/kg in rats based on the results of this study.

1.2.4.2 28-day Repeated Dose Subacute Toxicity Study in Rats

The duration of repeated dose toxicity study will be extrapolated to human therapeutic duration. Thus, toxic effects related to test drug dose in long term administration and determination of NOAEL are very important in further clinical study. Four groups of rats were administered with 0, 750, 1500 and 3000 mg/kg /once daily p.o. for 28 days respectively. Moribundity/mortality, clinical signs, body weight, food consumption, ophthalmology, clinical pathology (including urinalysis, hematology and serum chemistry), gross necropsy, organ weight and histopathology, were evaluated on those experimental rats. No death nor severe side effects had been observed. However, some effects were considered treatment-related as shown in Table 8:

Table 8. Summary of 28-day repeated dose toxicity study in rats

Group	1	2	3	4
Dose (mg/kg/day)	0	750	1500	3000
Male				
Calcium (mg/dL)[1]	10.7 ± 0.7	10.8 ± 0.8	10.4 ± 0.9	9.6 ± 0.5*
Female				
Sodium (mEq/L)[2]	147.4 ± 1.8	148.1 ± 1.6	147.8 ± 1.8	150.5 ± 2.1*
Thymus weight (mg)	501.3 ± 122.9	449.4 ± 91.7	418.4 ± 66.7	377.2 ± 81.2*

Reference range: [1]: 10.5~12.2; [2]: 136~156
*: $p < 0.05$

Concluded by the investigating institute, those abnormal are mild and did not influence the physical condition of experimented rats. Therefore, NOAEL for PDC-1421 in rats under this study condition is 3000 mg/kg/day.

1.2.4.3 28-day Repeated Dose Subacute Toxicity Study in Dogs

In order to determine NOAEL in dogs, PDC-1421 was repeatedly administered to 4 groups of dogs at dose levels of 0, 300, 1000, 3000 mg/kg once daily for 28 days. Soft feces were found in male dogs at 3000 mg/kg. There are several differences of physical value, lower mean corpuscular volume and monocytes in males and lower cholesterol and triglyceride in females, between test groups and control group, but these effects are not treatment-related or dose-dependent and within DCB (Development Center for Biotechnology) historical data range. Therefore, NOAEL for PDC-1421 in dogs is set at 3000 mg/kg.

1.2.4.4 Genotoxicity

Three studies, including Ames test, micronucleus test and chromosome aberration assay, were conducted to evaluate the genotoxicity of PDC-1421. In Ames test, five different strains of *Salmonella typhimurium* were used to evaluate the mutagenic potential when incubated at different concentration of PDC-1421. No mutation induced by PDC-1421 was observed. In micronucleus test, three dose of PDC-1421 at 500, 1000, 2000 mg/kg p.o. were administered to three different groups of BALB/c mice and the ability of PDC-1421 to induce micronucleated reticulocytes in mouse peripheral blood was measured. The results of this study indicated that PDC-1421 posed-negative response to clastogenic micronucleated reticulocytes in mice. In chromosome aberration assay, clastogenic activity was evaluated in Chinese hamster ovary (CHO) cells after adding the different concentration of PDC-1421. Based on the results of this study, chromosomes in CHO cells are not affected by PDC-1421. In conclusion, PDC-1421 does not pose any risk of genotoxicity.

1.3 Results of Clinical Trial Study of PDC-1421

1.3.1 Phase I Clinical Trial

In phase I trial, all total of 85 subjects were screened at study site and 30 subjects were enrolled. They were 9 subjects in cohort A with 7 administered PDC-1421 (380 mg) and 2 administered placebo, 1 of 7 PDC-1421 subjects (P01) had no laboratory test data at baseline; 8 subjects in cohort B with 6 administered PDC-1421 (1140 mg) and 2 administered placebo; 4 subjects in cohort C with 3 administered PDC-1421 (2280 mg) and 1 administered placebo; 9 subjects in cohort D with 7 administered PDC-1421(3800 mg) and 2 administered placebo, 1 of 7 PDC-1421 subjects (P27) had abnormal laboratory data at screening visit.

Physical examination was determined to be “normal” on every Body System in each cohort and no subject had DLT and toxicity grade.

All of the changes of vital signs from baseline of PDC-1421 and placebo group were mild and did not exceed the limit of normal range. Furthermore, all of the toxicity grades of vital signs were the lowest, systolic blood pressure in grade 1, increase >20 mm/Hg than baseline at 4 hours. No medical intervention/therapy was required. There were no correlation of changes from baseline or changes in the toxicity grade of vital signs between

doses of PDC-1421.

All changes of laboratory test data from baseline of PDC-1421 group were mild and no clinically significant deviation from the normal range. Furthermore, the toxicity grades of laboratory test data of PDC-1421 and placebo groups were the lowest, grade 1. No medical intervention/therapy was required. There were no correlation of change from baseline or change in the toxicity grade of laboratory test between doses of PDC-1421. Only two grade 2 toxicity (at 24 hours in glucose in cohort A and at 4 hours in glucose in cohort B) occurred in placebo group and no medical intervention/therapy were required for these cases.

ECG was determined to be “normal” in each time point and in each cohort. No subject had DLT and toxicity grade.

C-SSRS were all 0 point on Suicidal ideation, Intensity of ideation, Suicidal behavior in each cohort.

No subject had serious adverse event and no subject discontinued due to adverse event, no clinically significant finding in physical examinations, vital signs, electrocardiogram, laboratory measurements, and C-SSRS was observed throughout the treatment period, and the oral administration of PDC-1421 in healthy volunteers was safe and well-tolerated for the dose from 380 mg to 3800 mg. During the treatment period, 5 subjects reported to experience 8 mild adverse. The severity of these 8 adverse events was all mild and no medical action required. There was no correlation between number, severity, relationship and outcome of adverse events found between doses of PDC-1421 and placebo. Further, there was no clinically significant finding in electrolyte level and gastrointestinal discomfort during monitoring in the clinical trial. There were two mild adverse events such as lower heart rate and higher systolic blood pressure. In the dog telemetry study, only lower heart rate was found but not higher systolic blood pressure.

1.3.2 Phase II part I Clinical Trial in ADHD patients

This Phase II Part I was a single center, open label, dose escalation evaluation with two dosage levels in six subjects. The primary objective of this study was to determine the

effective doses and treatment period of PDC-1421 Capsule in adult subjects with ADHD. The secondary objective was to evaluate the safety of PDC-1421 Capsule in subjects receiving PDC-1421 at various dose levels.

The study screened 8 potential subjects. Two subjects, 11-001 and 11-004, were screened failures because they were unable to commit to follow weekly visits. Six subjects were enrolled in the study. All enrolled subjects were received the low-dose (1 capsule of PDC-1421 TID) of PDC-1421 capsules for 4 weeks and all of them were received the high-dose (2 capsule of PDC-1421 TID) of PDC-1421 capsules for next 4 weeks after passing the Checkpoint #1 for safety. A total of 6 subjects completed the study and no subject withdrew from the study after enrolment. The safety population included 6 subjects, the ITT population included 6 subjects, and the PP population included 5 subjects in the study. The study conclusions are as follows,

1. For the primary endpoints, the percentages of improvement of 40% or greater in ADHD-RS-IV score from baseline to 8 weeks treatment were 83.3% (N=5) in the ITT population and 80.0% (N=4) in the PP population.

2. For the secondary endpoints, a statistically significant improvement in the ADHD index subscale and Impulsivity subscale of CAARS-S:S at Week 8 compared to baseline was occurred. The mean changes in CAARS-S:S from baseline to 8 weeks treatment were -10.8 (P=0.0313) and -15.2 (P=0.0313) in the ITT population, and 10.6 (P=0.0625) and -14.0 (P=0.0625) in the PP population.

3. In the both ITT and PP population, the percentages of CGI-ADHD-I score of less than or equal to 2 at Week 8 were 100% (N=6 for ITT, N=5 for PP). The percentages of CGI-ADHD-S score of less than or equal to 2 at Week 8 were 33.3% (N=2) for ITT population and 60% (N=3) for PP population.

4. Regarding the safety profile, no deaths or severe adverse events occurred. Most of adverse events were rated as mild to moderate and recovered without actions, indicating PDC-1421 Capsule was safe and well tolerance. Moreover, treatment of PDC-1421 did not increase any risks in terms of laboratory data, vital sign, physical examination, suicidal ideation and suicidal behavior during its treatment and follow-up period.

1.4 Potential Risk and Benefit

1.4.1 Potential Risk

The toxicological profile of PDC-1421 was characterized in single and repeat oral dose studies of up to 90 days in rats and repeat oral dose studies of up to 28 days in dogs. Genetic toxicology and safety pharmacology have also been conducted. PDC-1421 was observed to be associated with some adverse effects in serum electrolytes and GI function, but none were clinically significant. Therefore, potential risks of PDC-1421 are fluctuated electrolyte level and gastrointestinal discomfort. We monitored these in the Phase I and Phase II study in MDD and ADHD patients, and there was no deviation of electrolyte level. But there were more gastrointestinal discomfort, such as dry mouth, comparing to the placebo during monitoring in the clinical trial. However, there were non-clinically significant mild lower diastolic blood pressure and lower heart rate in dog telemetry study, and it has been only with the 2500 mg/kg, which is around the NOAEL for dogs. The cardiovascular systems will be monitored in the clinical study.

1.4.2 Potential Benefit

According to nonclinical study results, the results of two *in vitro* assays support the fact that PDC-1421 is a selective norepinephrine reuptake inhibitor and have low affinity to serotonin and dopamine. A SHR animal model have shown that PDC-1421 have potential to develop as an ADHD medication. Furthermore, PDC-1421 will not pose the adverse effects caused by the molecules which possess anticholinergic or antihistamine activities due to its selectivity on norepinephrine transporter. The result of Phase II Part I showed that 5 out of 6 patients achieved the primary endpoint that the improvement of 40% or greater in ADHD Rating Scale-Investigator Rated (ADHD-RS-IV) from baseline up to 8 weeks treatment.

1.4.3 Risk Benefit Ratio

Potential risks in nonclinical results outlined above are minor and easy to monitor. Even though there were adverse events in phase I and Phase II trial in MDD and ADHD patients, no similar findings were found in nonclinical studies. The subsequent trial could be benefited from gathering further safety and efficacy information for PDC-1421 treatment in ADHD patients.

1.5 Dosage Regimen

Based on the FDA's guidance documents, NOAELs from toxicity studies were used to estimate the starting dose in our study. Table 10 summarizes the MRSD for 60 kg human/day calculated from the NOAEL of 28 day repeating dose studies in rats and in dogs using safety margin at 75-fold.

Table 10. Calculation of starting dose

Study	Species	Dosage	HED	Dose for 60 kg human/day
28-day repeated dose subacute oral toxicity study in rats	rat	3000 mg/kg (NOAEL)	483.9 mg/kg	387 mg/day (MRSD)
28-day repeated dose subacute oral toxicity study in dogs	dog	3000 mg/kg (NOAEL)	1666.7 mg/kg	1333 mg/day (MRSD)

Based on these calculations, we proposed the starting dose of PDC-1421 to be at 380 mg/day. In the phase I study, a single dose of PDC-1421 (oral administration) was used to evaluate the safety when taken by healthy subjects. The starting dose and dosage regimen are:

380 mg PDC-1421 (one capsule of PDC-1421 Capsule) once daily after meal

The dose escalation as follows.
Cohort A (one capsule; 380 mg):

Cohort A enrolled 9 subjects. Seven subjects received PDC-1421 Capsule and two received placebo. There was only one of placebo subjects who met a DLT due to the glucose value at 24 hours after drug administration. We continued the study to the next higher dosage, cohort B.

Cohort B (three capsules; 1140 mg):

Cohort B enrolled 8 subjects. Six subjects received PDC-1421 Capsule and two received placebo. There was only one of placebo subjects who met a DLT due to the glucose value at 4 hours after drug administration. We continued the study to the next higher dosage, cohort C.

Cohort C (six capsules; 2280 mg):

Cohort C enrolled 4 subjects. Three subjects received PDC-1421 Capsule and one

received placebo. There was no DLT in this cohort. We continued the study to the next higher dosage, cohort D.

Cohort D (ten capsules; 3800 mg):

Cohort D enrolled 9 subjects. Seven received PDC-1421 Capsule and two received placebo. There is no DLT in the final cohort.

Based on the results, the maximum tolerated dose (MTD) is ≧3800 mg of PDC-1421 Capsule so that the safe and well-tolerated for PDC1-421 Capsule is from 380 mg to 3800 mg.

According to studies in mouse model system to evaluate efficacious dose, SHR animal model, PDC-1421 was indicated to be efficient at oral administration of 675 mg/kg doses which are equivalent to about intraperitoneal injection of 5 mg/kg atomoxetine. The consideration is the course of treatment of atomoxetine, ADHD medication which is also a selective NRI, need one to three weeks for a good therapeutic response. There will be lower effective dose when long-term administration. The positive control, atomoxetine administrated by intraperitoneal injection in SHR animal model, and the absorption is better than oral. Base on the bioavailability is 63%, and the minimum starting dose is 0.5 mg/kg of Strattera (the trade name of atomoxetine), we translate the starting dose of PDC-1421 is 42.56 mg/kg (675 [mg] * 63% * 0.5 [mg/kg] / 5 [mg/kg] = 42.56 mg) and the human equivalent dose is about 2553.59 mg in 60 kg weight.

$$\frac{\text{PDC-1421 Recommended Dose in Human}}{\text{PDC-1421 Effective Dose in SHR}} = \frac{\text{Atomoxetine Starting Dose in Human by oral}}{\text{Atomoxetine Effective Dose in SHR by oral}}$$

(Assumption: Atomoxetine's bioavailability by oral is 63% by injection in SHR.)

According to the result of phase I trial and preclinical study with SHR animal model, we choose 1140 mg (3 capsules) and 2280 mg (6 capsules) as the dosage regimen of Phase II trial.

1.6 Compliance with Protocol, Good Clinical Practice (GCP)

and Applicable Requirement

This study and all operating procedures will be conducted in accordance with GCP guidelines, protocol and all applicable regulatory requirements issued by US FDA, to protect the rights, safety and well-being of the studying subjects.

1.7 Description of the Population to be Studied

We chose patients with Attention Deficit Hyperactivity Disorder as our subjects in this phase II trial.

2. Trial Objective

The primary objective of this trial was to determine the effective doses and treatment period of PDC-1421 Capsule in subjects with ADHD. The secondary objective was to evaluate the safety of PDC-1421 Capsule in subjects receiving PDC-1421 at various dose levels.

3. Trial Design

3.1 General Design

Table 11. Summary of general design

	Phase II Part II
Design	Double-blind, randomized, parallel group, placebo-controlled
ADHD patients	Stage I: 69 Stage II: 30
Treatment	Randomly assigned on a 1:1:1 basis to one of the three arms: (1) 1 PDC-1421 Capsule plus 1 placebo TID (2) 2 PDC-1421 Capsule TID (3) 2 Placebo TID for 56 days There will be an interim analysis between stage I and stage II.
Assessment interval	Biweekly
Efficacy and safety evaluation	• Primary endpoint: efficacy measurement (ADHD-RS-IV) • Secondary endpoints: other efficacy and safety measurements (ADHD-RS-IV, CAARS-S:S, CGI-I, E-SCT, ECG, vital sign, physical examination, hematology, blood chemistry and concomitant medication evaluation)

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 II study is 99 subjects who met the intent-to-treat basis.

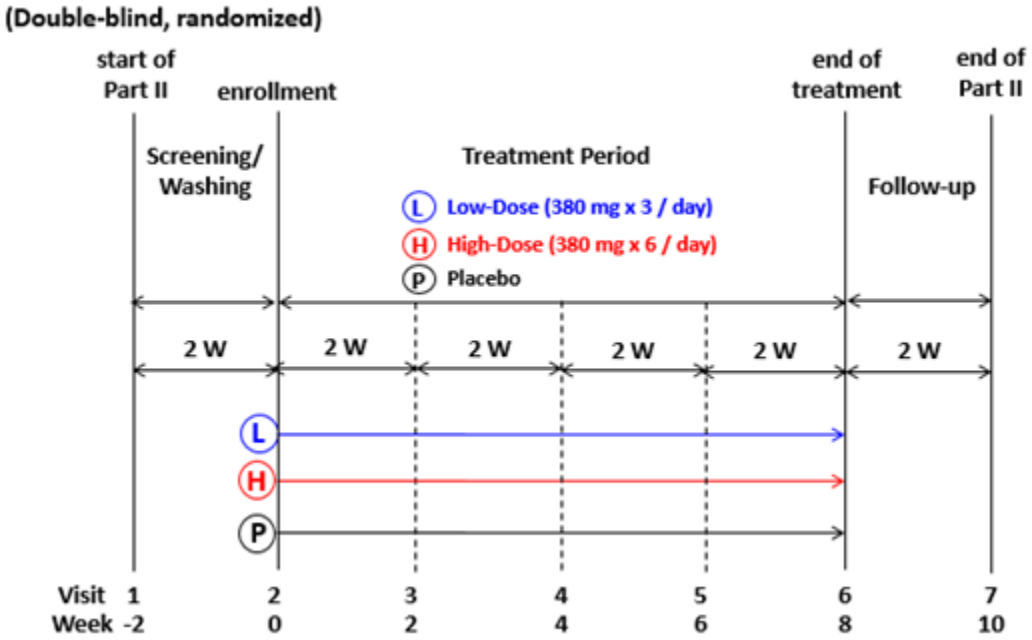
Part II is a randomized, double-blind, placebo-controlled, parallel-group study.

Stage I: Sixty nine 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). Each subject will be treatment for 8 weeks and will return for visit biweekly during the treatment period.

An interim analysis: An interim analysis will be conducted to evaluate the efficacy of PDC-1421 and to decide whether it is necessary enter the second stage of Part II. (See Section 8 for evaluation details.)

Stage II: Thirty 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). Each subject will be treatment for 8 weeks and will return for visit biweekly during the treatment period.

Figure 2. General design of procedure



3.2 Primary Endpoint

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

3.3 Secondary Endpoint

Table 12. The secondary efficacy endpoints in part II

Number	Items
1	Symptom remission in ADHD Rating Scale-Investigator Rated (ADHD-RS-IV total score ≤ 18) up to 8 weeks treatment.
2	Change from baseline in the ADHD Rating Scale-Investigator Rated (ADHD-RS-IV), Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (CAARS-S:S) and Empirical-Sluggish Cognitive Tempo (E-SCT) score up to 8 weeks treatment.
3	Clinical Global Impression - improvement (CGI -I) score of 2 or lower up to 8 weeks treatment.

3.4 Randomization and Blinding

Table 13. Summary of randomization and blinding

	Phase II Part II
Randomization	Randomized; 1 PDC-1421 Capsule plus 1 placebo TID: 2 PDC-1421 Capsules TID: 2 placebo TID = 1:1:1
Blinding	Double-blind; (1) Unblinding for interim analysis with the required information that predefined for interim statistical analysis (2) Unblinding at the end of trial and share his/her information of randomization if asked by the subject(s) (3) Emergency unblinding at a serious adverse event.

The randomization scheme generated by computer will be prepared by the CRO prior to the start of the study. In the study, subjects will be randomly allocated to the group of one of PDC-1421 Capsule (3 or 6 capsules) or placebo in a ratio of 1:1:1. All subjects and medical staff will be blinded to the treatment assigned till the end of the trial. All

emergency unblinding (e.g., due to a serious adverse event) should be reported immediately to the BioLite, Inc. Codes linking randomization number to actual treatment for each subject will be secured in a sealed, opaque envelop and maintained in the study site and research department of BioLite, Inc. The unblinding for interim analysis will be conducted by CRO only.

3.5 Investigational Drug

Investigational drug (PDC-1421 Capsule or placebo) will be maintained and dispensed by study sites. No one but the Investigator and/or his/her designee is permitted to access the investigational drug.

3.5.1 Dosage Form and Strength

PDC-1421 Capsule: 380 mg PDC-1421/capsule
Placebo: 380 mg corn starch/capsule

3.5.2 Manufacturer

ITRI (Industrial Technology Research Institute), Hsinchu county, Taiwan

3.5.3 Route of Administration

Oral administration

3.5.4 Dosing Regimen, packing and labeling

3.5.4.1 Dosing Regimen

Subjects will be assigned with a random number to be allocated into 3 treatment groups on a 1:1:1 basis and treated as following dose regimen:

- **Placebo:** 2 placebo capsules thrice daily for 56 days (8 weeks).
- **Low-Dose:** 1 placebo capsule and 1 PDC-1421 Capsule, thrice daily for 56 days (8 weeks).
- **High-Dose:** 2 PDC-1421 Capsules thrice daily for 56 days (8 weeks).

Dosing regimen for each part of the study is summarized with drug packing on

Table 14.

3.5.4.2 Packaging

Investigational drug (PDC-1421 Capsule or placebo) are provided by BioLite, Inc. and stored in the sites. Subjects will receive the investigational drug at visit 2 to visit 5 and also be requested to return unused drug at visit 3 to visit 6. Drug packing of the study is summarized with dosing regimen on Table 14.

- **Placebo:** Subjects will receive a drug bag with 42 + 6 (reserve) drug packs at visit 2 to visit 5. Each drug pack contains 2 placebo capsules. Biweekly visits start from visit 2, and will be requested during this 56-day treatment period.
- **Low-Dose:** Subjects will receive a drug bag with 42 + 6 (reserve) drug packs at visit 2 to visit 5. Each drug pack contains 1 placebo capsule and 1 PDC-1421 Capsule. Biweekly visits start from visit 2, and will be requested during this 56-day treatment period.
- **High-Dose:** Subjects will receive a drug bag with 42 + 6 (reserve) drug packs at visit 2 to visit 5. Each drug pack contains 2 PDC-1421 Capsules. Biweekly visits start from visit 2, and will be requested during this 56-day treatment period.

Table 14. Summary of dosing regimen and packaging

Part no.		**Part II**		
Dosing/Arm		**Placebo**	**Low-Dose**	**High-Dose**
Treatment Duration		56 days	56 days	56 days
Dosing Regimen	**Placebo**	2 Caps. TID	1 Cap. TID	0
	PDC-1421	0	1 Cap. TID	2 Caps. TID
Packaging		2 Placebo Caps./pack 42 + 6 packs /bag	(1 Placebo Cap. + 1 PDC-1421 Cap.)/pack 42 + 6 packs/bag	2 PDC-1421 Caps./pack 42 + 6 packs/bag
Visit Frequency		Biweekly		
No. of Drug bags Received / Visit		1		

3.5.4.3 Labeling

The drug bag of investigational drug will be clearly labeled as following:

For Part II:

Test Drug: PDC-1421 Capsule/placebo Amount: 48 packs (6 reserved packs included; 2 capsules/pack) Drug Bag Number: Subject Number: Visit No.: Study Protocol: BLI-1008-002 Drug Appearance: Brown capsule Major Component: Each capsule contains 380 mg of PDC-1421 or placebo Dosing: 1 pack (2 capsules) thrice daily after meal for 14 days and with extra 2 day for reserved Storage Condition: Store at a dry place at room temperature (15~25℃) Lot Number: Manufacturer: Industrial Technology Research Institute Date of Expiration: Sponsor: BioLite, Inc. Clinical Sites: "Caution: New drug - Limited by Federal Law to investigational use".
試驗藥物: PDC-1421 膠囊/安慰劑 數量: 48 包小藥包 (含 6 包備用小藥包，每包小藥包含 2 顆膠囊) 藥物編號: 受試者編號: 回診次別: Visit 計劃書編號: BLI-1008-002 藥物外觀: 棕色膠囊 主成份: 每顆膠囊含有 380 mg PDC-1421 或安慰劑 劑量: 三餐飯後服用 1 包小藥包(2 顆膠囊)，14 日份 (外加 2 日備用藥) 儲存條件: 儲存於乾燥常溫之環境 (15~25℃) 批號: 製造商: 工業技術研究院 有效日期: 廠商: 萊特先進生醫股份有限公司 試驗機構: "Caution: New drug - Limited by Federal Law to investigational use".

3.5.5 Study Drug Storage

Investigational drugs will be stored in a locked cabinet at room temperature (15~25 ℃) in the study sites.

3.6 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.

4. Subjects Selection and Withdrawal

Inclusion and exclusion criteria are as follows.

4.1 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-5)
6. A total score of 28 or higher of ADHD Rating Scale-Investigator Rated (ADHD-RS-IV) at screening
7. Have a moderate or severe symptom of ADHD with score of 4 or higher in Clinical Global Impression- Severity (CGI-S) at screening

4.2 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

4.3 Subject Recruitment and Screening

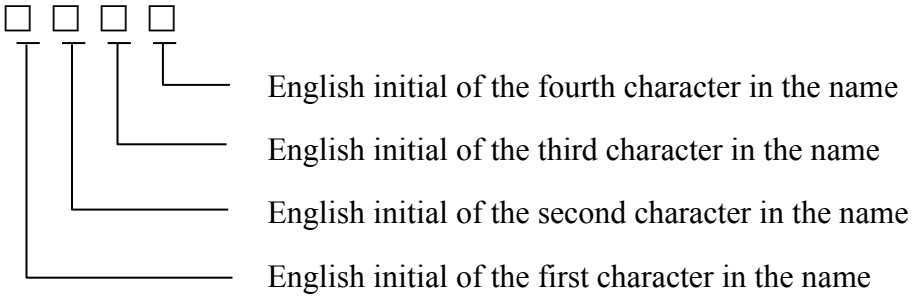
At Visit 1, Investigator will introduce the proposed clinical study to subjects who are interesting in this study. If a subject is willing to undergo an informed consent process based on GCP and participate in this study, the subject will be examined as described in section 5.2. At Visit 2, based on Visit 1 measurements, subject who meets the recruitment criteria will be enrolled in this study.

4.4 Subject Identification

In order to protect each subject's privacy, only subjects' initials will be used as part of subjects' identifications. In addition, a subject number will be assigned to each subject who signed the ICF and each subject who is eligible to enroll in the study.

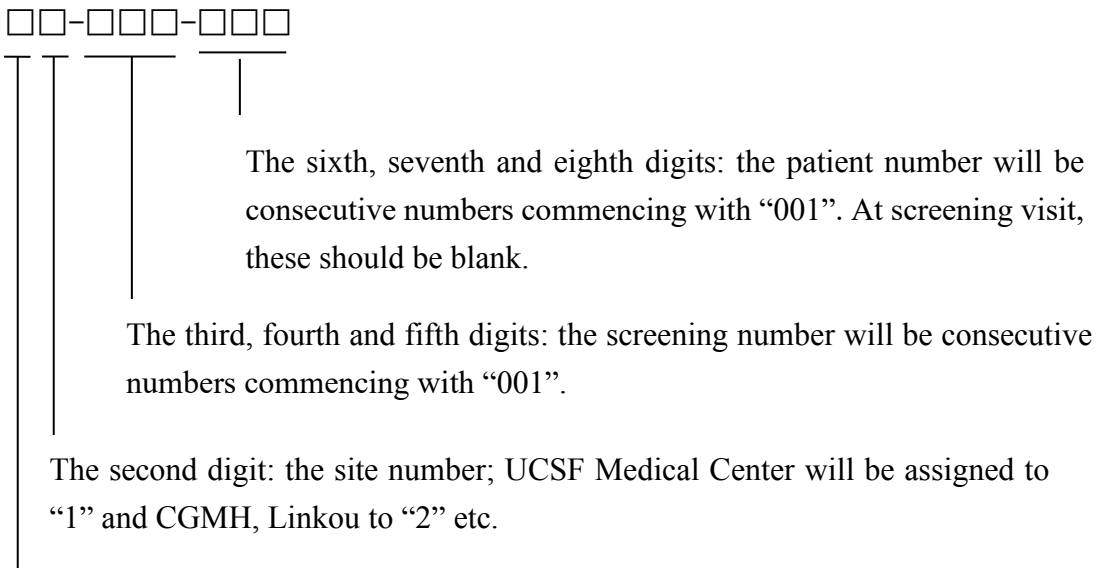
4.4.1 Subject Initial Allocation

A subject's initial will be assigned to each subject by the clinical research coordinator (CRC). Remain blank in the 3rd and 4th space if there have no more initial(s) to be filled in.



4.4.2 Subject Number Allocation

Each subject will be assigned a number by the CRC. All subject numbers will have six digits.



4.5 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(s) consider 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.

5. Treatment of Subjects

5.1 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*. The detailed information of PDC-1421 Capsule is described in section 1.1.

5.2 Treatment Schedule

Potential subjects will be introduced by Investigator or his/her designee 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.

Subjects met eligibility criteria will be assigned with a random number to be allocated into 3 treatment groups on a 1:1:1 basis and treated as following dose regimen:

- **Placebo:** 2 placebo capsules thrice daily for 56 days (8 weeks).
- **Low-Dose:** 1 placebo capsule and 1 PDC-1421 Capsule, thrice daily for 56 days (8 weeks).
- **High-Dose:** 2 PDC-1421 Capsules thrice daily for 56 days (8 weeks).

Subjects will be assessed biweekly (Visit 3, 4, 5, and 6). After the end of study treatment, subjects will be requested to return after two weeks for a follow-up (Visit 7). Screening, safety and efficacy assessments will be performed as Table 15.

During the COVID-19 public health emergency or similar events, the assessments of CAARS-S:S, CGI, ADHD-RS-IV, E-SCT, C-SSRS, AE evaluation, Concomitant Medication, Physical examination and Vital sign can be conducted by telephone, video, or email, but those remote assessments should be documented. All COVID-related changes will be pre-approved by the applicable IRBs.

Table 15. Part II-schedule of assessments

	Screening	Treatment Period					Follow-up
Visit	1	2	3	4	5	6	7
***Week**	-2 to 0	0	2	4	6	8	10
Informed consent	√						
Subject information	√						
Medical history	√						
DSM-5	√						
CAARS-S:S	√	√	√	√	√	√	√
CGI- S	√	√					
CGI- I			√	√	√	√	√
ADHD-RS-IV	√	√	√	√	√	√	√
E-SCT	√	√	√	√	√	√	√
C-SSRS	√	√	√	√	√	√	√
Concomitant medication	√	√	√	√	√	√	√
Physical examination	√					√	
Vital sign	√	√	√	√	√	√	√
ECG	√					√	
Laboratory examination							
Pregnancy test	√						√
Hematology	√	√		√		√	
Blood chemistry	√	√		√		√	
Eligibility evaluation	√						
Drug accountability		√	√	√	√	√	
AE/SAE evaluation		√	√	√	√	√	√

*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.

5.2.1 Screening Phase (Visit 1)

The Screening phase will be done within 0-2 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, race, 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-5, CAARS-S:S , CGI- S , ADHD-RS-IV, E-SCT, 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

5.2.2 Part II.- Treatment Period (Visit 2~6)

Subjects who meet the eligibility criteria will be enrolled and take study drugs. At visits 2 to 5, each subject will be dispensed a supply of study drug sufficient for next 2-week treatment period. The subjects will be instructed to take one dose (i.e., two capsules) after a meal thrice daily. Drug compliance is important for the safety and efficacy evaluations. Study coordinator needs to make sure drug adherence of the subjects is at least

80% during the treatment period. Otherwise, study coordinator(s) must report a protocol deviation including lower than 80% compliance and over 100% compliance during the treatment period. At visits 2, 3, 4, 5 and 6, the safety and efficacy parameters will be evaluated by the following items. Baseline data will be collected before dosing study drug.

- 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 (Only at visit 6)
- Hematology: RBC, WBC, platelets, hematocrit, hemoglobin, prothrombin time (PT), partial thromboplastin time (aPTT). (Only at visit 2, 4 and 6)
- 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 and 6)
- CAARS-S:S , CGI- -S (only for Visit 2) , CGI -I (only for Visit 3 – 6) , ADHD-RS-IV, E-SCT, C-SSRS and concomitant medication evaluation.
- AE/SAE evaluation
- Drug accountability

5.2.3 Follow-up (Visit 7)

Follow-up visit will be performed at visit 7 after two weeks of the last dose administration. The test items are outlined in the following:

- Pregnancy test
- Vital sign: heart rate, blood pressure, body temperature
- CAARS-S:S, CGI -I , ADHD-RS-IV, E-SCT, C-SSRS and concomitant medication evaluation
- AE/SAE evaluation

5.3 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, including MAOIs (monoamine oxidase inhibitor), NRIs (norepinephrine reuptake inhibitor) and norepinephrine receptor

agonist/antagonist. Subjects cannot 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:

1. Subjects who indicate that they can discontinue will be washed out for 1 week, and then allowed to begin study protocol;
2. 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.)

6. Efficacy Assessments

6.1 Specification of the efficacy parameters

Efficacy parameters are outlined as follows:

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

6.2 Methods and Timing for Assessing, Recording, and Analyzing of Efficacy Parameters.

The data obtained from eligible subjects before study drug administration in Visit 2 or Visit 1 (if no data at Visit 2) are set as baseline. After the beginning of treatment, the collection of data of efficacy parameters are performed at planned treatment schedule as section 5.2. CRC shall record these data in CRF in detail after each visit during the treatment period. In part II, data comparison between group of 1 capsule TID, 2 capsules TID of PDC-1421 Capsule and 2 capsules TID of placebo will be conducted in final report of this study to evaluate which group(s) of PDC-1421 Capsule are efficient. The rating scales are as follows:

- **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[15]. 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.

- **Clinical Global Impression**[16]

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 at all ill) to 7 (among the most extremely ill). 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).

- **CAARS-S:S**

Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (Conners et al., 1998; CAARS-S:S). This 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; and D: problems with self-concept) as well as a 12-item ADHD index can be computed[14]. The raw scores were converted into standard T-scores by SAS program which designed according to the Profile form of CAARS QuikScore forms. A T-score is a standard score with a mean of 50 and a standard deviation of 10 in all samples and across all scales.

- **E-SCT**

The E-SCT rating scale queries 15 Sluggish Cognitive Tempo symptoms rated from 0 = Never or Rarely, 1 = Sometimes, 2 = Often, 3 = Very Often, grouped into latent factors of daydreaming, working memory problems, and subjective sleepiness/tiredness. The scale was empirically derived from a set of 44 candidate

items [17]. Sluggish Cognitive Tempo has been shown to be a statistically related but distinct syndrome with respect to ADHD [18]. The range for the Total Score is 0-45. Factor scores are computed using this same method. For data analysis, mean item scores will be used to protect against missing data.

7. Safety Assessments

7.1 Specification of Safety Parameters

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

7.2 Methods and Timing for Assessing, Recording, and Analyzing of Safety Parameters

The data obtained before study drug administration in Visit 2 or Visit 1 (if no data at 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 5.2. AE or SAE will be closely monitored during the study period. CRC shall record these data in CRF in detail. In part II, data are recorded from screening stage to the last visit.

7.3 Adverse Events (AEs)

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, 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), therapy (no action, treatment given, withdrawn from study, temporarily

discontinued) and severity. Common Terminology Criteria for Adverse Events v4.03 (CTCAE Table 16) is a descriptive terminology and the grading (severity) scale is provided for each AE term.

Table 16. Common Terminology Criteria for Adverse Events

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.

7.4 Serious Adverse Events (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

7.5 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

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

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

7.6 SAE Report Procedure

7.6.1 Expedited Reporting of SAEs

Since the clinical study is to be carried out in U.S. and Taiwan, when expedited SAEs meet the informed criteria according to the relevant regulations, they will be reported to the Food and Drug Administration (FDA), U.S. and Minister of Health and Welfare (MOHW), Taiwan by the Sponsor. Written reports should be made on the ADR Reporting Form on Med watch 3500A Form of US FDA and of Taiwan MOHW, and submitted in a timely fashion according to all relevant regulatory requirements. A copy of this report will also be provided to the principal investigator's local institutional review board if necessary. All SAEs will be monitored until they are resolved or until the principal investigator assesses them as irreversible, chronic, or stable, or until the subject dies. During the clinical trial, if expedited SAEs occur, the investigator should inform the sponsor/CRO within 24 hours by fax and/or telephone.

7.6.2 IRB Notification

Reports of serious adverse events will be communicated to IRB:

- Fatal or life-threatening SUSAR: Should be reported to IRB in the 7 calendar days and detailed written documents should be provided within 15 days after being aware of the event.
- Non-Fatal or life-threatening SUSAR: Should be reported to IRB no later than 15

calendar days.

- Non-SUSAR SAE: Should be reported to IRB following each IRB regulations.

7.6.3 Record Retention

All telephone/fax reports must be followed with a written narrative summary of the adverse event and any sequel. These narratives, which confirm the information collected by telephone and may provide additional information not available at the time of the initial report, must be reviewed by the clinical monitor within 7 calendar days following the telephone/fax report to sponsor.

8. Statistic Methods

8.1 Sample Size Determination

In part II, this is a small proof-of-concept study to evaluate low-dosed PDC-1421 arm, high-dosed PDC-1421 arm and placebo arm in the treatment of ADHD. A two stage design developed by Jung (2008) with alpha=0.15 and power=80% will be used. We estimated that the PDC-1421 is considered non-effective if the response rate based on ADHD Rating Scale – Investigator Rated (ADHD-RS-IV) is 20 % or lower and is worth further study if the response rate is 40 % or higher. At the first stage, we recruit 23 subjects for each group. If the difference between the numbers of responders for any PDC-1421 arm and control arm is greater or equal to 0, we proceed to the second stage. We will recruit 10 subjects for each group at the second stage. If the difference between the accumulated numbers of responders for any PDC-1421 arm and control arm is less than 4, we reject the drug. The minimum sample size required is to recruit 69 subjects, while the maximum sample size is 99. No multiple comparison will be applied.

8.2 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 baseline demographic characteristics within each cohort will be compared using chi-square test or exact test for categorical variables and ANOVA (analysis of variance) or Kruskal-Wallis non-parametric ANOVA test for continuous variables. The primary endpoint will be analyzed by chi-square test, while the secondary endpoints will be analyzed using the ANOVA or Kruskal-Wallis non-parametric ANOVA test for continuous endpoints and chi-square test for binary endpoints. Since this is only a small proof-of-concept study, no multiple comparisons will be made to adjust the p-values for all pairwise comparisons.

8.3 Analysis of Efficacy and Safety

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 major protocol deviation. The major 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 patients who take at least one dose of study medication. The data are analyzed utilizing the last observation carried forward (LOCF) technique to impute the missing data.

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.

8.4 Premature Termination and Handling of Missing Data

Any premature termination of the study therapy will be recorded in CRF. Listing of the subjects with premature termination will be provided with the dates and reasons. Missing data caused by premature termination will be utilized the last observation carried forward (LOCF).

9. Quality Control and Quality Assurance

9.1 Study Monitoring

The clinical monitor from sponsor-designated contract research organization (CRO) will be responsible for overseeing the progress of a clinical trial to be conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirements. All written informed consent and CRFs will be carefully reviewed and the accuracy of the data will be validated by clinical monitor. The monitoring can be performed remotely, but it should be documented.

9.2 Sponsor Auditing

Prior to locking the database of safety, the representative of Sponsor's quality assurance department may visit the Investigator's site to implement an audit of study. The audit will to determine the compliance of Investigator with protocol, GCP and applicable regulations. Besides, auditors will assess the accuracy of clinical data record. The Investigator and trial personnel need to cooperate with auditor to facilitate the process of audit.

9.3 Inspected by Regulatory Authorities

Local regulatory authority may visit the Investigator to conduct an inspection of this study and the site. The Investigator must make the trial-related records accessible to regulatory agency inspectors. In addition, the Investigator needs to notify the Sponsor immediately when contacted with regulatory authority for the inspection.

10. Ethical Considerations

10.1 Confidential

All information about study subjects will be kept confidential in accordance with the applicable regulatory requirement, to protect and respect the privacy of study subjects. Only the members performed study-related processes, including trial-related monitoring, audits, IRB/IEC review, and regulatory inspection, could directly access to source data/documents.

10.2 Protocol Amendment

Any amendment to the Protocol which deemed necessary as the study progresses will be fully discussed by Investigators and the Sponsor. A written amendment must be submitted to US FDA and TFDA and the respective Chairman of the IRB, except when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in clinical monitors or change of telephone numbers). Investigator must wait for their approvals of the protocol amendment before implementing the changes. A protocol change intended to eliminate an apparent immediate hazard to trial subjects may be implemented immediately while simultaneously informing FDA /IRB and TFDA/IRB.

When, in the judgment of Chairmen of the IRB, Investigator and/or the Sponsor, the amendment to the Protocol substantially alters the study design and/or increases the potential risk to the subjects, the currently approved written informed consent form will be modified according to the modification. A second informed consent will be obtained from subjects enrolled in the study before further participation.

10.3 Informed Consent

Written informed consent must be reviewed and approved by IRB. Informed consent will be designed to provide detailed information, including explanation of the purpose of this study, the risks and discomforts involved, potential benefits and all basic elements

required by regulatory agencies, to participants. Investigator (or his or her qualified designees) will be responsible for explaining the contents of the informed consent to participants as clear as possible. Once it is felt that the subject understands the implications of participating, the written informed consent form shall be signed by the subject and a witness. The written informed consent will be obtained from each subject before any study related procedures (including any pre-treatment procedures) are performed.

10.4 Institutional Review Board (IRB)

This study is conducted to be consistent with the principles of the Declaration of Helsinki and GCP. This protocol and any supplementary documents, including written informed consent form, subject recruitment advertisements and Investigator's Brochure, must be reviewed and approved by IRB qualified with local legal prescriptions prior to study initiation. The members of IRB are average thirty people, including medical doctors, professors of pharmacology and members whose primary area of interest is in the nonscientific area such as law and social welfare policy. One group of members of IRB meet once a month. Any changes in protocol must be received the IRB approval/favorable opinion in advance of use except for the immediate hazards to trial subjects. Investigator shall submit a status report to IRB at the end of the study. IRB must be notified by the Investigators promptly for all unanticipated problems involving risk to human subjects or others. Investigator is required to maintain an accurate and complete record of all written submissions made to IRB and must agree to share all such documents and reports with the Sponsor and any regulatory agency.

11. Data Handling and Record Keeping

An EDC (electronic data capture) system may be used in this study to handle data in an electronic CRF. Follow the EDC system guideline when using it.

11.1 Data Handling and Collection

11.1.1 Study Specific Binders

Two types of binder will be utilized in this study:

- Subject Binder: Containing informed consent and certain source documents collected for each subject entered the treatment period of the study. Each Subject Binder will have tab dividers for the laboratory printouts. Subject Binders will be kept at each study center.

- Investigator Study File: Documents pertinent to the conduct of this study will be filed in this binder.

11.1.2 Responsibilities of Investigators

The Investigator shall process, prepare and maintain complete and accurate study procedure and documentation in compliance with GCP standards and local laws, rules and regulations. It is the Investigators' responsibility to ensure that the designated CRC for this study at the hospital fully understands his/her responsibilities and has the ability to fulfill all the relevant tasks on behalf of the Investigator in many occasions. For each subject enrolled, a CRF must be completed and signed by the Investigator, no matter if this subject has completed the study or not. The Investigator agree to fully cooperate and assist the clinical monitor in performing their duties, including enabling direct access to the relevant hospital and clinic records. Study documentation will be promptly and fully disclosed to the Sponsor by the Investigator and also shall be made available at the Investigators' site for inspection, copying, review and audit for a reasonable number of times by representatives of the Sponsor or any regulatory agencies. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit

to correct the known error in the study documentation and case report forms. The Investigator shall submit to the Sponsor all original case report forms and all reports required by the Protocol when the clinical study have been completed or terminated.

11.1.3 Responsibilities of Clinical Monitor

Clinical monitor shall frequently inspect the source documents (clinic and hospital subject records) and compare them with the CRF at regular time interval throughout the study, to verify the adherence of study execution to the Protocol and confirm the completeness, consistency and accuracy of the data entered. The monitor will perform source data verification by visually comparison between the entries of the CRF and subjects' records, including informed consent, inclusion/exclusion criteria, key variables, drug administration, adverse experience records and safety variables. Additional monitoring will be required if the error rate is unacceptably high.

11.2 Records Retention

11.2.1 Source Document Retention

Source documents refer to any record pertained to a given subject in the study from which study data is, or could be, obtained or verified. This includes, but not limited to, records, charts, notes and laboratory reports. These records, maintained by the Investigator, shall comply with applicable regulations. At the aspect of ICF keeping, one of the original signed informed consent forms for each participant shall be filed with records kept by the Investigator and the other copy should be given to the subject. Besides, progress notes on each visit to the clinic will be required. The progress note of each visit shall at least contain the date of the visit, a general reference to the procedures completed, general subject status remarks including any significant medical findings, and the signature of the clinician making the entry. In addition, any contact with the subject via telephone or other means that provides significant clinical information, such as adverse events, will also be documented in the progress notes. These will be filed with subject records kept by the Investigator and made available for inspection by authorized personnel.

11.2.2 CRF Retention

All information required by the Protocol will be collected on either CRF or source documents. Essential documents should be retained until the Sponsor informs the Investigator that documents are no longer need to be kept.

11.2.3 Record Maintenance

Regulation requires all investigators participating in clinical trials to maintain detailed clinical data for the duration of one of the following periods, whichever is shortest:

(1) A period of at least two years following the approval date of an application for a marketing permit in support of which the results of the clinical investigation were submitted, or

(2) A period of two years after the Sponsor notifies the Investigator that no further application is to be filed with the regulatory authority.

The Investigator will not dispose of any record relevant to this study without informing the Sponsor and providing an opportunity for the Sponsor personnel to collect such record. The Investigator shall take full responsibility for maintaining all documentation related to the conduct of this study, including subject records, research data, and pertinent correspondence. These documents are subject to inspection by the Sponsor and appropriate regulatory authorities.

11.3 Investigator Study File Management

It will be the responsibility of the clinical monitors/CRC to maintain the Investigator Study File. The Investigator Study File for this study will contain, but not limited to, the information listed below:

(1) Investigator Brochure.
(2) Signed Protocol and Amendments approved by both FDA/TFDA and IRB.
(3) Copies of FDA/TFDA and IRB approval letter for this study.

(4) Curricula Vitae of Investigator and sub-investigator.

(5) Other documentation of IRB complied with FDA/TFDA regulations.

(6) Copy of Informed Consent Form approved by both FDA/TFDA and IRB.

(7) All IRB correspondence (reports to IRB, including reports of all death and adverse experience, annual progress reports, final reports, acknowledgement of receipt of report and actions taken by IRB).

(8) All IND Efficacy and Safety Reports sent to the Investigator.

(9) Laboratory certification and/or license.

(10) All written correspondence with the Sponsor.

(11) Normal ranges of laboratory value for all laboratory tests required by Protocol.

(12) CRA monitoring logs.

(13) Drug Invoices and Drug Dispense/Return Records.

12. Publication Plan

Sponsor and Investigator will determine authorship and govern other aspects of the publication process related to this trial. All publications must be approved by the Sponsor prior to publication.

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