STUDY PROTOCOL

A Phase I Dose-Escalation Study in Healthy Volunteers to Evaluate the Safety and Tolerability Profiles of Careseng 1370

Protocol Number: Careseng 1370-01

Investigational Product: Careseng 1370 granule 4,000 mg/Sachet

Sponsor: [redacted]

Version: 5.0, Sep 18, 2020

Confidentiality Statement

This protocol is provided for the purpose of conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines.

Principal Investigator:

Title:

Affiliation:

Address:

TEL:

Signature: _____ Date: _____ (dd-mmm-yyyy)

PROTOCOL APPROVAL PAGE

Protocol Number: Careseng 1370-01

Version: 5.0

Date: 18SEP2020

Protocol Title: A Phase I Dose-Escalation Study in Healthy Volunteers to Evaluate the Safety and Tolerability Profiles of Careseng 1370

Sponsor Approval(s):

[redacted]

Signature Date

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Graft
CRO	Contract research organization
DLT	Dose limiting toxicity
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case report form
γ-GT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IP	Investigational product
IQR	Inter-quartile range
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
MedDRA	Medical Dictionary for Regulatory Activities
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observable-adverse-effect level
PI	Principal investigator
PPD	20(S)-protopanaxadiol
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SD	Sprague-Dawley
SOP	Standard operation procedure
WBC	White blood cell

TABLE OF CONTENTS

PROTOCOL SUMMARY

Full Title	A Phase I Dose-Escalation Study in Healthy Volunteers to Evaluate the Safety and Tolerability Profiles of Careseng 1370
Short Title	Careseng 1370 for Healthy Volunteers
Investigational Product	Careseng 1370 granule 4,000 mg /Sachet
Active Ingredients	DS-1370 powder (dry extracts of *Panax notoginseng* stems and leaves)
Protocol No	Careseng 1370-01
Study Phase	Phase I
Sponsor	[redacted]
Objectives	**Primary objective** The primary study objective is to explore the safety and tolerability profiles of Careseng 1370 as single agent based on dose limiting toxicity (DLT) observed in healthy volunteers. The results will be employed for future study to determine the maximal tolerated dose (MTD) of Careseng 1370 to treat chemotherapy-induced myelosuppression in advanced non-small cell lung cancer (NSCLC) patients. DLT is defined as any ≥ Grade 2 adverse event from Day 1 to Day 10 (DLT observation period), causally at least possibly related to Careseng 1370 administration as judged by the investigator. The grading system applied in this study is "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[12] (Appendix 1), issued by United States Food and Drug Administration in September 2007. The definition of Grade 5 (death) was added to this grading system as it was not defined in the guidance (Section 8.2 and Appendix 1). **Secondary objective** The secondary study objective is to evaluate the pharmacokinetic profiles of marker ingredient in Careseng 1370, 20(S)-protopanaxadiol (PPD), and its metabolites in healthy volunteers.

Study Design

This study will be performed in healthy volunteers in a conventional 3+3 dose-escalation design. There are total 4 cohorts in this study. Three cohorts (level A, B, and C) of up to 6 evaluable volunteers per cohort planned to be sequentially accrued to receive Careseng 1370 1, 2, and 3 sachets per day, 4,000 mg/sachet before meal (starting from 1 sachet, level A). One cohort (level D, modified cohort) of up to 6 evaluable volunteers per cohort will be planned to be accrued to receive 1 sachet of Careseng 1370 every other day (level D) when the dose de-escalates from level A. At least 5 days of staggering and with the investigator's judgement of no safety concern will be required to administer the next volunteer for the first three volunteers of each cohort. The staggering time starts from Day 1 of one volunteer to Day 1 of the next volunteer. Careseng 1370 should be taken around 1 hour before meal where the respective number of sachets and meals of each dose level are as follows:

- Level A (1 sachet): 1 sachet before breakfast
- Level B (2 sachets): 1 sachet before breakfast, 1 sachet before lunch
- Level C (3 sachets): 1 sachet before breakfast, 2 sachets before lunch
- Level D (1 sachet) (modified cohort): 1 sachet before breakfast on 1st, 3rd and 5th days

Note:

1. Breakfast is defined as the first meal of the visit day while lunch is defined as the 2nd meal of the visit day in this study.

2. The modified cohort is the lower dose level below the starting dose level A. This cohort (level D) will be implemented when the dose de-escalates from level A.

The starting dose of Careseng 1370 (level A) is determined based on the results of the preclinical toxicity studies. Based on these data, the starting dose of Careseng 1370, 1 sachet containing 652 mg drug substance, is considered to be a safe starting dose in human. When the dose de-escalation was determined on level A, the modified cohort (level D) will be implemented. Volunteers will be followed from the start of Careseng 1370 administration up to Final visit (Day 22).

In dose-escalation, if 0 of the first 3 evaluable volunteers enrolled at a given dose level experiences DLT, then dose escalation will proceed to the next cohort of volunteers after the Data and Safety Monitoring

	Board (DSMB) agrees unless it is at the highest dose level. If 0 of the first 3 evaluable volunteers enrolled at the highest dose level experience DLT or if DLT occurs in exactly 1 of the first 3 evaluable volunteers within a given dose cohort, the cohort will be expanded and 3 additional evaluable volunteers will be enrolled subsequently at that dose level. In the expanded cohort, if ≤ 1 of 6 evaluable volunteers experiences DLT, escalation to the next dose level or study completion (if at the highest dose level) will proceed after the DSMB agrees. If more than 1 evaluable volunteer (≥ 2 of 3 or ≥ 2 of 6 evaluable volunteers) at any given dose level experiences DLT, then no further dose escalation will occur. For such situation, unless it is at the lowest dose level of Careseng 1370 (level D), if DLT appears in 1 of 6 evaluable volunteers of the preceding cohort, then the MTD will be the preceding dose, which is essentially the highest dose cohort if ≤ 1 DLT was observed in all dose cohorts. If the number of evaluable volunteers is 3 in the preceding cohort, then 3 more evaluable volunteers will be added to the preceding cohort. If DLT appears in > 1 volunteer in the expanded preceding cohort, then the next lower dose cohort will be checked. If 2 of 4 or 5 evaluable volunteers experience DLT in the expanded cohort, the DSMB will determine to grant dose de-escalation based on the safety of the proceeding dose level without enrolling the next volunteer in the cohort. No dose level below pre-specified lowest dose level will be tested for this study. No volunteer is allowed to be assigned to more than 1 dose level. All decisions for dose escalation/de-escalation will be made by the DSMB.
Study Population	Healthy volunteers aged 20-40 years old (inclusive)
Number of Volunteers	Planned 4 cohorts of up to 6 evaluable healthy volunteers for each cohort, up to 24 evaluable healthy volunteers in total. Around 29 eligible healthy volunteers will be recruited to complete up to 24 evaluable healthy volunteers. *Note: A volunteer is considered evaluable if he/she* *1. receives any Careseng 1370, and* *2. experiences DLT OR completes DLT observation period with at least 80% of study drug compliance and has exposed to Careseng 1370 for at least 4 days (level A, B and C), OR completes DLT observation period with 100% of study drug compliance (level D).*

Study Product, Dose, Route, Regimen	**Four dose cohorts are arranged for this study:** - Dose level A: Careseng 1370 1 sachet before breakfast for consecutive 5 days - Dose level B: Careseng 1370 1 sachet before breakfast and 1 sachet before lunch for consecutive 5 days - Dose level C: Careseng 1370 1 sachet before breakfast and 2 sachets before lunch for consecutive 5 days - Dose level D (modified cohort): Careseng 1370 1 sachet before breakfast on 1st, 3rd and 5th days The duration of dosing time between breakfast and lunch from Day 2 to Day 5 should be as close to those for Day 1. Volunteers should take Careseng 1370 for lunch (if there is one) at 4 hours (+ 10 minutes) after taking Careseng 1370 for breakfast on that day. *Note: Careseng 1370 generally should be taken around 1 hour before respective meal.*
Duration of Administration	Healthy volunteers will take Careseng 1370 following the study schedule (level A, B, and C: consecutive 5 days; level D: 1st, 3rd and 5th days), or until experiencing DLT, unacceptable toxicity, his/her loss of follow-up, or early withdrawal, whichever comes first.
Recruitment Strategies	Local posters are planned for recruitment of volunteers. Other acceptable methods of recruiting volunteers may include advertisement in magazine and social media, which should be submitted to IRB for review and approval before the recruitment efforts begin.
Volunteer Assignment	This study will be done in healthy volunteers administered with Careseng 1370 1, 2, or 3 sachets per day (level A, B, and C), or Careseng 1370 1 sachet on 1st, 3rd and 5th days (level D) before meal in the conventional 3+3 design. No volunteer is allowed to be assigned to more than 1 dose level.
Study Visits	**Screening visit:** within 2 weeks before Day -1 (inclusive) **Hospitalization:** - Day -1: registration of hospitalization in the evening **Dosing visits:**

- Day 1: approximately 24 hours of hospitalization (pre-dose PK blood sampling and dosing at site for breakfast and lunch)
- Day 2: discharge from hospitalization (pre-dose PK blood sampling and dosing (if scheduled) at site for breakfast and at home for lunch)
- Day 3 pre-dose PK blood sampling and dosing at site for breakfast and at home for lunch
- Day 4: pre-dose PK blood sampling and dosing (if scheduled) at site for breakfast and at home for lunch. Registration for hospitalization after planned dosing (if scheduled) on Day 4

Note:

1. *The definition of "pre-dose" means the timing prior to the first dose of that day (level A-D), or the timing for examinations scheduled on that day (2nd and 4th days of level D)*
2. *The definition of "pre-dose PK blood sampling" means blood collection for PK prior to the first dose of that day (level A-D), or at scheduled visits without dosing of that day (level D). Time points for pre-dose PK blood sampling on Day 2 to Day 5 should be as close as that on Day 1.*
3. *The definition of "dosing at home for lunch" means that subjects leave the site and administer the second dosing somewhere else before lunch except level A and D (off-site dosing). Subjects are required to come back to the site in the evening for hospitalization on Day 4.*

- Day 5: hospitalization (pre-dose PK blood sampling, dosing at site for breakfast and lunch, and post-dose PK blood sampling (level A and D: 0.5, 1, 2, 4, 6, 12 hours after dosing on Day 5; level B and C: 0.5, 1, 2, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16 hours after the 1st dose on Day 5))

Follow-up visits:

- Day 6: post-dose PK blood sampling for 24 hours, discharge from hospitalization
- Day 7: post-dose PK blood sampling for 48 hours
- Day 8: post-dose PK blood sampling for 72 hours
- Day 12 (±2)

	Note: The definition of "post-dose PK blood sampling" means blood collection for PK after the 1st dose on Day 5. **Final visit:** Day 22 (±2) or within 3 days after withdrawal is confirmed
Volunteers Inclusion Criteria	A healthy volunteer is eligible for the study if all of the followings apply: 1. Adult aged between 20-40 years old (inclusive) 2. Physically and mentally healthy volunteer as confirmed by an interview, medical history, clinical examination, chest X-rays, and electrocardiogram. Volunteer with non-clinically significant signs or symptoms may be eligible at investigator's discretion. 3. Body Mass Index (BMI) between 18.5 and 24, inclusive (BMI will be calculated as weight in kilogram [kg]/(height in meters)^2 [m^2]) 4. Clinically normal hematology, biochemistry and urinalysis determinations based on investigator's discretion. Volunteer with non-clinically significant signs or symptoms may be eligible at investigator's discretion. 5. Volunteer is willing and able to comply with study procedures and sign informed consent prior to initiation of any study-mandated procedures.
Volunteers Exclusion Criteria	Any volunteer meeting any of the exclusion criteria will be excluded from study participation: 1. Volunteer who has a history or evidence of a medical condition that would expose them to a risk of a significant adverse event or interfere with the assessments of safety or pharmacodynamics variables during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, immune, neurological, musculoskeletal or hematological disease as determined by the clinical judgment of the investigator 2. Volunteer has received any other investigational agent within 4 weeks prior to the first dose of study drug 3. Volunteer has taken or potentially takes any herbal medication/supplements/medicinal food, prescription medication and/or over-the-counter medication within 2 weeks prior to the first

dose of study drug

4. Volunteer has consumed alcohol, caffeine, grapefruit juice, nicotine, phosphorous supplement, calcium supplement, or food rich in calcium within 24 hours prior to the first dose of study drug

5. Female volunteer of childbearing potential who:
   - is lactating; or
   - has positive pregnancy test result at eligibility checking; or
   - refuses to adopt at least two forms of birth control (at least one of which must be a barrier method) from Screening visit to Final visit.

   Note:

   Acceptable forms include:

   1. Established use of oral, injected or implanted hormonal methods of contraception.

   2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

   3. Barrier methods of contraception: Condom OR Occlusive cap (diaphragm or cervical/vault caps)

6. Male volunteer with female spouse/partners who are of childbearing potential refuses to adopt at least two forms of birth control (at least one of which must be a barrier method) from Screening visit until Final visit

7. Known or suspected allergy or hypersensitivity to any ingredients of study product

8. With history of stroke, myocardial infarction, or Coronary Artery Bypass Graft (CABG) surgery within the last 6 months prior to the screening visit

9. With history of cardiac failure (New York Heart Association class 2 or above), unstable angina, or life-threatening arrhythmia within the last 6 months prior to the screening visit

10. With blood pressures as systolic blood pressure < 90 mmHg or > 170 mmHg or diastolic blood pressure < 50 mmHg or > 120 mmHg at eligibility checking

11. History of psychiatric disorder

12. History of left ventricular outflow obstruction, such as aortic stenosis and hypertrophic cardiomyopathy

	13. With a history of human immunodeficiency virus (HIV) infection or hepatitis B or C infection 14. Plan to receive surgery from Screening visit until Final visit 15. Known or suspected hypersensitivity to any component of Careseng 1370, including components in plants of genus *Panax*, Tween 80, Kolliphor® P188, Fujicalin, and ginseng flavor
Primary Endpoint	Incidence of adverse events (AEs) and serious adverse events (SAEs)
Secondary Endpoints	1. Changes from baseline to applicable post-dosing visits in vital signs, physical examination, body weight, EKG, and laboratory examination results. Baseline will be the value of measurement closest to and before start of IP administration. 2. Pharmacokinetic parameters of marker ingredient in Careseng 1370, 20(S)-protopanaxadiol (PPD) and its metabolites
Exploratory endpoints	Change in lymphocyte activity (based on CD3, CD4, CD8, CD19, CD16 and CD56 assessments, presented as CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD16+/CD56+, and CD4/CD8 ratio) on Day 2, Day 6 and Day 22 compared to baseline
Withdraw Criteria	Healthy volunteers may be withdrawn from the trial due to any of the following conditions: 1. Volunteer decides to withdraw his/her informed consent. 2. Volunteer experiences intolerable symptoms. 3. Any pathological event, clinical adverse event, or any change in the volunteer's status giving indication to the investigator that further participation in the study may be harmful to the volunteer's health. 4. Volunteer becomes pregnant from Screening visit until Final visit. 5. Volunteer develops DLT. 6. Volunteer is lost to follow-up or dies. 7. Volunteer misses dosing and fails to reach 80% of study drug compliance, does not keep appointments, or otherwise does not adhere to protocol requirements.

Statistical Analysis

Analysis population

The following populations are defined for statistical analysis:

Intent-to-treat (ITT) population:

- Volunteers receive any Careseng 1370

Demographic analysis, safety evaluation and pharmacokinetic analysis will be performed on the ITT population. Decision of the MTD will be made based on DLT observation of evaluable subjects.

Statistical Analysis

Baseline characteristics, including demographic data such as gender, age, etc., will be presented using descriptive statistics and displayed by dose level (levels A to D).

Additionally, descriptive statistics will be provided for all of the endpoints by dose level. Frequency table will be provided for categorical data, while mean, standard deviation, maximum, minimum, median, inter-quartile range (IQR), and 95% two-sided confidence interval (for data change from the baseline) will be calculated for continuous measurements.

Adverse events observed after signing informed consent form till exit from study will be coded, by using Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by dose level by System/Organ/Class and Preferred Terms classified in MedDRA as appropriate. The toxicity grade of adverse events will be rated according to “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”[12] defined in Section 8.2 and Appendix 1. Findings in physical examinations will be displayed for each individual system. Changes from pre-dosing laboratory test results, body weight, EKG and vital signs to applicable post-dosing visits will be analyzed by descriptive statistics and (if applicable) will be presented by transition table for normality (normal, clinically not significant, clinically significant). Findings in 12-Lead EKG and X-ray will be presented by description.

SCHEDULE OF ASSESSMENTS

Period	Screening[1]	1st Hospitalization							1st Discharge	Dosing	2nd Hospitalization															2nd Discharge	Follow-up			Final[9]	Unscheduled Visit[10]
Visit	V1	V2							V3	V4~V5	V6															V7	V8	V9	V10	V11	NA
Target Day	-14 to -1	-1	1						2	3~4	4[14]	5														6 (24±2 hrs post-dose)	7 (48±2 hrs post-dose)	8 (72±2 hrs post-dose)	12 (±2)	22 (±2) or within 3 days after withdrawal	NA
		Registration	Pre-dose *	Dosing	Post-first dose (hr)						Registration	Pre-dose *	Dosing	Post-dose (hr)																	
					1	4	8	12						0.5	1	2	4	4.5	5	6	7	8	9	10	12	16						
Informed Consent	X																														
Identifier Number	X																														
Medical History	X																														
Medication History	X																														
Demographics	X																														
Height	X																														
Body Weight	X		X[2]						X[2]	X[2]		X[2]														X			X	X	At investigator's discretion
Physical Examination	X		X[2]				X[4]		X[2]	X[2]		X[2]					X[4]									X			X	X	
Vital Signs	X		X[2]		X[4]	X[4]	X[4]		X[2]	X[2]		X[2]					X[4]									X			X	X	
12-lead EKG	X[13]		X[2]		X[4]	X[4]	X[4]	X[4]	X[12]	X[12]		X[2]			X[4]		X[4]				X[4]			X[4]		X			X	X	
Laboratory Tests[3]	X[2, 13]						X[4]		X[2]	X[2]		X[2]					X[4]									X[2]			X[2]	X[2]	
Chest X-ray	X[13]																														
Pregnancy Test	X																													X	
Inclusion/Exclusion Criteria	X		X[2]																												
Pre-dose PK Blood Sampling[5]			X[2]						X[2]	X[2]		X[2]																			
Post-dose PK Blood Sampling: Level A and D[6]														X	X	X	X			X					X	X						
Post-dose PK Blood Sampling: Level B & C[7]														X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Dosing at Study Site[8]				X					X	X			X																		

Period	Screening[1]	1st Hospitalization	1st Discharge	Dosing	2nd Hospitalization	2nd Discharge	Follow-up			Final[9]	Unscheduled Visit[10]
Visit	V1	V2	V3	V4~V5	V6	V7	V8	V9	V10	V11	NA
Diary and/or Drug Dispensing[8]	X	X	X	X	X	X					
Diary and/or drug Return[8]			X	X	X	X	X				
Concomitant Medication	----------										
Adverse Events[11]	----------										

* The definition of "pre-dose" means the timing prior to the 1st dose of that day (level A-D), or the timing for examinations scheduled on that day (2nd and 4th days of level D).

1. Screening visit can be on the same day as Day -1 if healthy volunteers meet the entry criteria at Screening visit. The eligibility checked on Day 1 will be based on the results of body weights, physical exam, vital signs, and 12-lead EKG of Day 1 as well as other information collected during Screening visit.
2. Healthy volunteers should come fasted for these measurements prior to Careseng 1370 administration (pre-dose measurement, Day 1 to Day 5), and prior to breakfast (Screening, Day 6, Day 12, and Day 22).
3. Healthy volunteers should come fasted for laboratory examinations at all scheduled time points, except 8 hours post-first dose on Day 1, and 4 hours post-dose on Day 5. Laboratory examination to be measured in this study will consist of the following:
   - Hematology: hemoglobin, hematocrit (Hct), RBC, WBC (with differential), absolute neutrophil count (ANC), lymphocyte count, platelets, international normalized ratio (INR) of prothrombin time, activated partial thromboplastin time (APTT).
   - Biochemistry: AST, ALT, albumin, alkaline phosphatase (ALP), total bilirubin, creatinine, blood urea nitrogen (BUN), c-reactive protein, total protein, gamma glutamyl transferase (γ-GT), blood glucose, uric acid, total cholesterol, triglycerides, sodium, potassium, calcium, magnesium, phosphorus, amylase, lipase
   - Urinalysis: pH, protein, RBC, WBC, casts
   - Immunology: CD3, CD4, CD8, CD19, CD16 and CD56 (presented as CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD16+/CD56+, and CD4/CD8 ratio, for Screening visit, Day 2, Day 6 and Day 22)
4. Time window of ±20 minutes is allowed.
5. The time point for pre-dose PK blood sampling is prior to the first dose of that day. Time points for pre-dose PK blood sampling on Day 2 to Day 5 should be as close as that on Day 1.
6. Time points for post-dose PK blood sampling after dosing on Day 5 for level A and D are as follows: 0.5 hour (± 5 minutes), 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 5 minutes), 12 hour (± 20 minutes), 24 (± 2) hours, 48 (± 2) hours, and 72 (± 2) hours.
7. Time points for post-dose PK blood sampling after the first dose on Day 5 for level B and C are as follows: 0.5 hour (± 5 minutes), 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 5 minutes), 4.5 hours (± 5 minutes), 5 hours (± 5 minutes), 6 hours (± 5 minutes), 7 hours (± 5 minutes), 8 hours (± 5 minutes), 9 hours (± 5 minutes), 10 hours (± 5 minutes), 12 hour (± 20 minutes), 16 hour (± 20 minutes), 24 (± 2) hours, 48 (± 2) hours, and 72 (± 2) hours.
8. The dosing times for breakfast and for lunch from Day 2 to Day 5 should be as close to those for Day 1. Volunteers should take Careseng 1370 for lunch (if there is one) at 4 hours (+ 10 minutes) after taking Careseng 1370 for breakfast on that day. Volunteers will take the Careseng 1370 for administration for lunch at home on Days 2, 3, and 4 (except level A and D). Volunteers of level D will receive 1 sachet of Careseng 1370 every other day. Volunteers need to bring used and unused Careseng 1370 back at the next visit. The information to be collected in diary should contain at least the number of sachets taken together with respective dosing time for each day.
9. If possible, and after the withdrawal is consented or Careseng 1370 is discontinued, volunteers will be assessed using the procedures planned for the Final visit within 3 days.

10. Unscheduled visits may be conducted if clinically indicated. Items to be conducted will be decided at investigator's discretion.
11. Adverse events will be collected from informed consent is signed.
12. 12-lead EKG will be performed before and about 1 hour after Careseng 1370 administration for breakfast. Volunteers of level D will receive 12-lead EKG one time at scheduled visits when there is no scheduled dosing on that day.
13. 12-lead EKG, Chest X-Ray and laboratory test performed within 14 days are acceptable.
14. Subjects are required to return to the site for hospitalization on Day 4 after planned dosing on that day. This implementation aims to perform the planned procedures at the similar timing as those on Day 1.

1. BACKGROUND AND RATIONALE

1.1 General Introduction

Panax notoginseng (Burk.) F.H. Chen (*Panax notoginseng*) is a species of the genus *Panax*, family *Araliaceae*. Three species in this genus (*Panax ginseng* C.A. Meyer, *Panax quinquefolius* L. and *Panax notoginseng* (Burk.) F.H. Chen) are highly regarded as medicinal plants in China and the USA (Wen and Zimmer, 1996).[1] *Panax notoginseng* belongs to the same genus as Korean ginseng (*Panax ginseng* Meyer) and American ginseng (*Panax quinquefolius* L.), and their main components are similar (Li et al., 2014).[2] The root of *Panax notoginseng*, known as Sanqi or Tianqi in East Asian countries, is one of the primary herbs in traditional Chinese medicine. Sanqi, which has been widely used as a tonic and haemostatic drug for more than 400 years, still has an important place in today's regional market. With the increasing study of Chinese material medica, substantial efforts have been made to research the phytochemistry and pharmacological effects of *Panax notoginseng* and over 200 compounds have been isolated from *Panax notoginseng,* and a variety of pharmacological effects have been found.

Typical botanical characteristics of *Panax notoginseng* include growing to a height of 30–60 cm, dark green leaves branching from a stem and a cluster of red berries in the middle. The stems are upright, simple, erect and unbranched (Guo et al., 2010).[3] The main root is conical or cylindrical and ranges in length from 1 to 6 cm. The main root is taupe or drab yellow on the surface, with several wrinkles and root marks. Generally, *Panax notoginseng* is removed from the soil and dried before it blooms in autumn. It can be ground singly into powder that is swallowed or combined with other herbs (Committee for the Pharmacopoeia of China, 2010).[4] The distribution of *Panax notoginseng* is very narrow due to its sensitivity to sunlight. After a long period of evolution, it grows primarily in the Wenshan mountain area of Yunnan province. It has a narrow habitat located around N 23.5° and E 104° that ranges in altitude from 1200 to 2000 m. A large percentage of the raw materials in China is produced here (Guo et al., 2010).[3]

As for Ethnopharmacology, the root of *Panax notoginseng* has played an indispensable role in Chinese healthcare for a long time. It is the main ingredient in Yun Nan Bai Yao (雲南白藥), a famous haemostatic herbal remedy that is used to stop bleeding, decrease inflammation and relieve pain (Sun et al., 2010).[5] *Panax notoginseng* is also one of the sources of cardiotonic pill that has been used in China, Korean and Russia for the treatment of cardiovascular diseases, such as occlusive vasculitis, coronary diseases, atherosclerosis, and cerebral infarction (Zhao et al., 2006).[6] The initial description of this plant can be traced back to the Compendium of

Material Medica (《本草綱目》), written by Shi Zhen Li. In this classic book, *Panax notoginseng* was recorded to have the actions to stop bleeding, remove blood stasis, alleviate pain, and it could be applied to treat bleeding caused by swords or axes, as well as hemoptysis, hematemesis, epistaxis and blood dysentery. Then the subsequent book Supplements for Compendium of Material Medica(《本草綱目拾遺》), written by Xue Min Zhao, described the function of Sanqi as similar to that of *Panax ginseng* C. A. Meyer. The difference is that *Panax ginseng* C.A. Meyer is good for tonifying qi (氣), while *Panax notoginseng* is especially helpful for nourishing the blood. It is worthy to note that this tonic action, which is usually used in folk hasn't been written in Compendium of Material Medica(《本草綱目》) and many material medical books, and just can be found in few books, like New Compilation of Material Medica (《本草新编》) and Chinese Medicine Dictionary (《中國醫藥大辭典》). In the Chinese pharmacopoeia, the properties of this herb are described as warm in nature, sweet and slightly bitter in taste. It is attributive to the liver and spleen meridians, it has the actions to dissipate blood stasis, stop bleeding, promote blood circulation and alleviate pain, so it can be applied in haemoptysis, hematemesis, rhinorrhagia, haemafecia, metrorrhagia and metrostaxis, traumatic bleeding and pain caused by traumatic injury (Committee for the Pharmacopoeia of China, 2010).[4]

Because of its defined clinical effects, some formulas were created by ancient doctors. Nowadays, many prescriptions are in clinical use. There are nearly 60 kinds of Chinese patent medicines in the Chinese pharmacopoeia, and the forms including capsules, granules, tablets, pills, dripping pills, powders, etc., in which capsules and tablets are the most used forms (Shi et al., 2012).[7] Although *Panax notoginseng* have been used massively, there are over 1500 t of stems and leaves of *Panax notoginseng* were turned out every year, but less than 5% stems and leaves is to be used only.

The stems of *Panax notoginseng* and the leaves of *Panax notoginseng* demonstrate a certainty of clinical application of anti-tumor activity (Jiang et al., 2014).[8] The compositions and contents of saponins isolated from the leaves of *Panax notoginseng* are significantly different from the underground parts in that the leaves and stems of *Panax notoginseng*, mainly contain plentiful PPD-type saponins, such as ginsenosides Rb3, Rb1, Rc, and notoginsenoside Fc (Wang et al., 2016).[9] Furthermore, chemical profile indicates the leaves of *Panax notoginseng* contain the marker saponins F2, 20(R)-Rg3, 20(S)-Rg3, and Rh2 (Wang et al., 2016),[9] and these compounds illustrate anti-proliferation effect on human colorectal cancer cells (Wang et al., 2007).[10]

In a myelosuppression attenuation study using DS1370 (same as drug substance DS-1370 used in this study), dry extracts of *Panax notoginseng* powder, 30 mice were divided into 5 groups, which were control group, docetaxel (Doc) + cisplatin (CP)

group, Doc + CP + DS1370 (1,072 mg/kg) group, Doc + CP + DS1370 (536 mg/kg) group, Doc + CP + DS1370 (268 mg/kg) group. Each groups included 6 mice. Doc (12 mg/kg) was injected to mice via intraperitoneal injection on Day 0, then, CP (12 mg/kg) was injected to mice via intraperitoneal injection 6 hours later, and sample DS1370 was administered by oral gavage from Day 1 to Day 5. The study results indicate sample DS1370 can attenuate the myelosuppression that caused by cisplatin and docetaxel injection. According to the results of peripheral blood cells count and bone marrow hematopoiesis ability, the effective doses of DS1370 are 536 mg/kg and 1072 mg/kg. Additionally, the dosages of DS1370 at 268, 536, and 1072 mg/kg are considered to be safe with employed chemotherapy as these dosages after chemotherapy did not cause further body weight reduction or tumor suppression on mice.[11]

1.2 Rationale and Justification for the Study

1.2.1 Rationale for the Study Purpose

Panax notoginseng has recently attracted pharmaceutical attention for its potential effects to treat myelosuppression. This phase I study is therefore proposed to evaluate the safety and tolerability profiles of Careseng 1370 as single agent in healthy volunteers as reference to determine recommended dose to treat myelosuppression for cancer subjects receiving chemotherapy in the future.

1.2.2 Rationale for Doses Selected

Based on the preclinical toxicity study, no-observed-adverse-effect level (NOAEL) of DS-1370 is determined as 675 mg/kg/day in rats of both genders, leading to human equivalent dose (HED) of 675/6.2 = 108.8 mg/kg/day. Considering choosing a safety factor of 10, the maximum recommended starting dose (MRSD) is 10.88 mg/kg/day, equivalent to around 653 mg/day for a 60-kg adult. The pharmacology data indicates that administration of DS-1370 536 mg/kg and 1,072 mg/kg (but not 268 mg/kg) daily are efficacious in treating myelosuppression caused by docetaxel and cisplatin in mice. The HED (divided by 12.3) based on 536 mg/kg is 43.58 mg/kg/day (2,614.63 mg/day for a 60-kg adult). Each Careseng 1370 sachet will be around 4,000 mg in weight containing powder of 652 mg DS-1370 (16.3% w/w) plus 3,348 mg of excipients (83.7% w/w). The MRSD will be one sachet per day and the anticipated therapeutic dose (ATD) range will be 4 to 8 sachets per day. One, two, and three sachets of Careseng 1370 per day (level A, B, and C) are therefore selected at Sponsor's discretion for this study. Consideration of

unexpected drug effects on human body, one modified cohort (level D) is planned as the lower dose level below the starting dose level A. The modified cohort (level D) will be implemented when the dose de-escalates from level A.

1.2.3 Rationale for Study Population

Healthy volunteers are recruited to explore the safety and tolerability profiles of Careseng 1370 for safety concern and as reference to determine recommended dose for cancer subjects receiving chemotherapy in the future.

1.2.4 Rationale for Study Design

Single arm, dose escalation of Careseng 1370 with traditional 3+3 paradigm will be employed to achieve the purpose of this study.

1.3 Potential Risks and Benefits

There will be no potential benefits for healthy volunteers to participate in this study.

Potential risks of Careseng 1370 are based on the toxicology findings in Sprague-Dawley (SD) rats. Possible influence on coagulation prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) was noted in both sexes of rats receiving mid- (1,350 mg/kg/day) and high-dose (2,700 mg/kg/day) for 13 weeks. But the prolonged PT and APTT were not seen at the end of recovery period in 2,700 mg/kg recovery animals. It was also noted that the mean body weights of mid- and high-dose male rats were 9.3% and 13.8% lower than that of the controls, respectively. Final mean body weight of high-dose recovery male rats was 11.8% lower than that of the controls. Final mean body weight gains of mid- and high-dose male rats were 15.7% and 23.2% lower than that of the controls. Final mean body weight gains of high-dose recovery males was 19.2% lower than that of the controls. Therefore, body weight loss and bleeding prolonged are possible risks that subjects in this study may experience.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary objective:

The primary study objective is to explore the safety and tolerability profiles of Careseng 1370 as single agent based on DLT observed in healthy volunteers. The results will be employed for future study to determine the MTD of Careseng 1370 to treat chemotherapy-induced myelosuppression in advanced non-small cell lung cancer (NSCLC) patients.

DLT is defined as any ≥ Grade 2 adverse event from Day 1 to Day 10 (DLT observation period), causally at least possibly related to Careseng 1370 administration as judged by the investigator. The grading system applied in this study is "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[12] (Appendix 1), issued by United States Food and Drug Administration in September 2007. The definition of Grade 5 (death) was added to this grading system as it was not defined in the guidance (Section 8.2 and Appendix 1).

Secondary objective:

The secondary study objective is to evaluate the pharmacokinetic (PK) profiles of marker ingredient in Careseng 1370, 20(S)-protopanaxadiol (PPD), and its metabolites in healthy volunteers.

2.2 Endpoints

2.2.1. Primary endpoints

Incidence of adverse events (AEs) and serious adverse events (SAEs)

2.2.2. Secondary endpoints

1. Changes from baseline to applicable post-dosing visits in vital signs, physical examination, body weight, EKG and laboratory examination results. Baseline will be the value of measurement closest to and before start of IP administration.

2. Pharmacokinetic parameters of marker ingredient in Careseng 1370, 20(S)-protopanaxadiol (PPD) and its metabolites

2.2.3. Exploratory endpoints

Exploratory endpoints in item 1 below are measured to explore the immunity

ability of Careseng 1370.

1. Change in lymphocyte activity (based on CD3, CD4, CD8, CD19, CD16 and CD56 assessments, presented as CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD16+/CD56+, and CD4/CD8 ratio) on Day2, Day 6 and Day 22 compared to the baseline

3. STUDY POPULATION

3.1 Volunteers Enrollment

In design of traditional 3+3 paradigm with four candidate dose levels, the number of evaluable healthy volunteers will be up to 24.

Note: A volunteer is considered evaluable if he/she

1. receives any Careseng 1370, and

2. experiences DLT OR completes DLT observation period with at least 80% of study drug compliance and has exposed to Careseng 1370 for at least 4 days (level A, B, and C), OR completes DLT observation period with 100% of study drug compliance (level D).

3.2 Inclusion Criteria

A healthy volunteer is eligible for the study if all of the followings apply:

1. Adult aged between 20-40 years old (inclusive)
2. Physically and mentally healthy volunteer as confirmed by an interview, medical history, clinical examination, chest X-rays, and electrocardiogram. Volunteer with non-clinically significant signs or symptoms may be eligible at investigator's discretion.
3. Body Mass Index (BMI) between 18.5 and 24, inclusive (BMI will be calculated as weight in kilogram [kg]/(height in meters)^2 [m^2])
4. Clinically normal hematology, biochemistry and urinalysis determinations based on investigator's discretion. Volunteer with non-clinically significant signs or symptoms may be eligible at investigator's discretion.
5. Volunteer is willing and able to comply with study procedures and sign informed consent prior to initiation of any study-mandated procedures.

3.3 Exclusion Criteria

Any volunteer meeting any of the exclusion criteria will be excluded from study participation:

1. Volunteer who has a history or evidence of a medical condition that would expose them to a risk of a significant adverse event or interfere with the assessments of safety or pharmacodynamics variables during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, immune, neurological, musculoskeletal or hematological disease as determined by the clinical judgment of the investigator

2. Volunteer has received any other investigational agent within 4 weeks prior to the first dose of study drug

3. Volunteer has taken or potentially takes any herbal medication/supplements/medicinal food, prescription medication and/or over-the-counter medication within 2 weeks prior to the first dose of study drug

4. Volunteer has consumed alcohol, caffeine, grapefruit juice, nicotine, phosphorous supplement, calcium supplement, or food rich in calcium within 24 hours prior to the first dose of study drug

5. Female volunteer of childbearing potential who:
   - is lactating; or
   - has positive pregnancy test result at eligibility checking; or
   - refuses to adopt at least two forms of birth control (at least one of which must be a barrier method) from Screening visit to Final visit.

   Note: Acceptable forms include:

   1. Established use of oral, injected or implanted hormonal methods of contraception.

   2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

   3. Barrier methods of contraception: Condom OR Occlusive cap (diaphragm or cervical/vault caps)

6. Male volunteer with female spouse/partners who are of childbearing potential refuses to adopt at least two forms of birth control (at least one of which must be a barrier method) from Screening visit until Final visit

7. Known or suspected allergy or hypersensitivity to any ingredients of study product

8. With history of stroke, myocardial infarction, or Coronary Artery Bypass Graft (CABG) surgery within the last 6 months prior to the screening visit

9. With history of cardiac failure (New York Heart Association class 2 or above), unstable angina, or life-threatening arrhythmia within the last 6 months prior to the screening visit

10. With blood pressures as systolic blood pressure < 90 mmHg or > 170 mmHg or diastolic blood pressure < 50 mmHg or > 120 mmHg at eligibility checking

11. History of psychiatric disorder

12. History of left ventricular outflow obstruction, such as aortic stenosis and hypertrophic cardiomyopathy

13. With a history of human immunodeficiency virus (HIV) infection or hepatitis B or C infection
14. Plan to receive surgery from Screening visit until Final visit
15. Known or suspected hypersensitivity to any component of Careseng 1370, including components in plants of *genus Panax*, Tween 80, Kolliphor® P188, Fujicalin, and ginseng flavor

3.4 Withdrawal Criteria

Healthy volunteers may be withdrawn from the trial due to any of the following conditions:

1. Volunteer decides to withdraw his/her informed consent.
2. Volunteer experiences intolerable symptoms.
3. Any pathological event, clinical adverse event, or any change in the volunteer's status giving indication to the investigator that further participation in the study may be harmful to the volunteer's health.
4. Volunteer becomes pregnant from Screening visit until Final visit. Volunteer's pregnancy status should be checked by serum or urine pregnancy test at Screening visit and Final visit and any time if investigator or volunteer suspects the volunteer is pregnant.
5. Volunteer develops DLT.
6. Volunteer is lost to follow-up or dies.
7. Volunteer misses dosing and fails to reach 80% of study drug compliance, does not keep appointments, or otherwise does not adhere to protocol requirements.

The reasons for withdrawal must be recorded in the electronic Case Report Form (eCRF) and in the volunteer's medical records for all early terminated cases. All study participants withdrawn from the study will be requested as possible to return for assessments scheduled at Final visit. If a volunteer is withdrawn due to an AE, every effort will be made to follow the event until the AE resolved or stabilized at a level acceptable to the investigator.

3.5 Concomitant Therapy

All medications, supplements, and herbal medicinal food taken by the study volunteer beginning four weeks prior to the Screening visit up to Final visit will be recorded on the appropriate page of the eCRF. This record will include the name of the medication,

frequency, unit dose, dates of the drug was started and stopped, and the indication for the use of the drug.

Prohibited therapies include the following:

1. Other investigational drugs within 4 weeks prior to Day 1 until Final visit
2. Other herbal medications/supplements/medicinal food within 2 weeks prior to Day 1 until Day 15
3. Prescription medication and/or over-the-counter medication within 2 weeks prior to Day 1 until Day 15
4. Alcohol, caffeine, grapefruit juice, nicotine, calcium or phosphorous supplement within 24 hours prior to Day 1 until Day 7
5. Food rich in calcium within 24 hours prior to Day 1 until Day 7, including dairy food, soymilk, tofu, black bean, clams, sardines, squid, cauliflower, kale, cabbage, Chinese mustard, basil, black sesame, seaweed, black jelly ear, calcium-fortified food, etc. A calcium-restricted diet plan designed for 4 different dose cohorts (Dose level A: 1,730 mg calcium/day; Dose level B: 960 mg calcium/day; Dose level C: 200 mg calcium/day, Dose level D: 1,730 mg calcium/day) will be provided to volunteers as a dietary guideline during this period of time
6. Any type of surgery from Screening visit until Final visit.

Additionally, volunteers will be advised to avoid ingesting excessive amount of food very rich in phosphorous during the dosing period, including yolk, animal organs, dried meat, dried seafood, grains, beans, nuts, royal jelly, coke, beer, yakult, chips, powder of milk, yeast, tea, or cocoa, etc.

4. STUDY DESIGN

This study will be performed in healthy volunteers in a conventional 3+3 dose-escalation design. There are total 4 cohorts in this study. Three cohorts (level A, B, and C) of up to 6 evaluable volunteers per cohort planned to be sequentially accrued to receive Careseng 1370 1, 2, and 3 sachets per day, 4,000 mg/sachet before meal (starting from 1 sachet, level A). One cohort (level D, modified cohort) of up to 6 evaluable volunteers per cohort will be planned to be accrued to receive 1 sachet of Careseng 1370 every other day (level D) when the dose de-escalates from level A. At least 5 days of staggering and with the investigator's judgement of no safety concern will be required to administer the next volunteer for the first three volunteers of each cohort. The staggering time starts from Day 1 of one volunteer to Day 1 of the next volunteer. Careseng 1370 should be taken around 1 hour before meal where the respective number of sachets and meals of each dose level are as follows:

- Level A (1 sachet): 1 sachet before breakfast
- Level B (2 sachets): 1 sachet before breakfast, 1 sachet before lunch
- Level C (3 sachets): 1 sachet before breakfast, 2 sachets before lunch
- Level D (1 sachet) (modified cohort): 1 sachet before breakfast on 1st, 3rd, and 5th days

Note:

1. Breakfast is defined as the first meal of the visit day while lunch is defined as the 2nd meal of the visit day in this study.

2. The modified cohort is the lower dose level below the starting dose level A. This cohort will be implemented when the dose de-escalates from level A.

The starting dose of Careseng 1370 (level A) is determined based on the results of the preclinical toxicity studies. Based on these data, the starting dose of Careseng 1370, 1 sachet containing 652 mg drug substance, is considered to be a safe starting dose in human. When the dose de-escalation was determined on level A, the modified cohort (level D) will be implemented. Volunteers will be followed from the start of Careseng 1370 administration up to Final visit (Day 22).

In dose-escalation, if 0 of the first 3 evaluable volunteers enrolled at a given dose level experiences DLT, then dose escalation will proceed to the next cohort of volunteers after the DSMB agrees unless it is at the highest dose level. If 0 of the first 3 evaluable volunteers enrolled at the highest dose level experiences DLT or if DLT occurs in exactly 1 of the first 3 evaluable volunteers within a given dose cohort, the cohort will

be expanded and 3 additional evaluable volunteers will be enrolled subsequently at that dose level. In the expanded cohort, if ≤ 1 of 6 evaluable volunteers experiences DLT, escalation to the next dose level or study completion (if at the highest dose level) will proceed after the DSMB agrees. If more than 1 evaluable volunteer (≥ 2 of 3 or ≥ 2 of 6 evaluable volunteers) at any given dose level experiences DLT, then no further dose escalation will occur. For such situation, unless it is at the lowest dose level of Careseng 1370 (level D), if DLT appears in 1 of 6 evaluable volunteer of the preceding cohort, then the MTD will be the preceding dose, which is essentially the highest dose cohort if ≤ 1 DLT was observed in all dose cohorts. If the number of evaluable volunteers is 3 in the preceding cohort, then 3 more evaluable volunteers will be added to the preceding cohort. If DLT appears in > 1 volunteer in the expanded preceding cohort, then the next lower dose cohort will be checked. If 2 of 4 or 5 evaluable volunteers experience DLT in the expanded cohort, the DSMB will determine to grant dose de-escalation based on the safety of the proceeding dose level without enrolling the next volunteer in the cohort. No dose level below pre-specified lowest dose level will be tested for this study.

No volunteer is allowed to be assigned to more than 1 dose level. All decisions for dose escalation/de-escalation will be made by the DSMB.

4.1 Randomization and Blinding

Randomization and blinding will not be applied.

4.2 Termination of Study

The study will be terminated if (1) study medication is considered not tolerable even in the lowest dose cohort by ≥ 2 of 3 or ≥ 2 of 6 evaluable volunteers, (2) the sponsor terminates the study.

The sponsor reserves the right to terminate the study at any time. The appropriate IRB/IEC and regulatory authorities should be informed accordingly.

4.3 Dose Delay and Discontinuation Rules

Healthy volunteers will discontinue Careseng 1370 if experiencing DLT or intolerable toxicity. If volunteers in level A, B or C happen to miss or delay dosing not owing to DLT or intolerable toxicity, volunteers may continue the next dosing. If volunteers in level D happen to miss or delay dosing not owing to DLT or intolerable toxicity, volunteers should be withdrawn from the study. For level A, B and C, volunteer who misses dosing and fails to reach 80% of study drug compliance should be withdrawn from the study. For level D, volunteer who misses any dosing should be withdrawn from the study.

If possible, volunteers will be assessed using the procedures planned for the Final visit within 3 days after withdrawal is consented or Careseng 1370 is discontinued.

5. TRIAL MATERIALS

5.1 Trial Product

[redacted]

Product name	Careseng 1370
Character	Light yellow granule 4,000 mg/sachet
Composition (w/w)	[redacted]

5.2 Dosage and Administration

Four dose cohorts are employed for Careseng 1370 oral administration in healthy volunteers:

- Dose level A: Careseng 1370 1 sachet before breakfast for consecutive 5 days
- Dose level B: Careseng 1370 1 sachet before breakfast and 1 sachet before lunch for consecutive 5 days
- Dose level C: Careseng 1370 1 sachet before breakfast and 2 sachets before lunch for consecutive 5 days
- Dose level D (modified chort): Careseng 1370 1 sachet before breakfast on 1st, 3rd and 5th days

The duration of dosing time between breakfast and lunch from Day 2 to Day 5 should be as close to those for Day 1. Volunteers should take Careseng 1370 for lunch (if there is one) at 4 hours (+ 10 minutes) after taking Careseng 1370 for breakfast on that day.

Note: Careseng 1370 generally should be taken around 1 hour before respective meal.

5.3 Storage and Drug Accountability

The IP shipping is to be arranged by the sponsor/designee to the study site and to be handled by the investigator/designee or the designated pharmacist for management and dispensation. Careseng 1370 sachets should be stored at controlled temperature of 15 (59°F) to 30°C (86°F). Long-term exposure to bright light should be avoided. All of the used and unused Careseng 1370 sachets will be returned from the clinical site to the sponsor unless prohibited by site policy. Each batch shipped, used, and returned from/to the sponsor to/from the clinical site will be recorded according to date to keep track of the Careseng 1370 sachets with precise details.

5.4 Packaging/Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person at sponsor with Standard Operating Procedures (SOPs) of sponsor, Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations. Careseng 1370 sachets will be packaged in aluminum foil/bags. All aluminum foil/bags for packaging study medication will be labeled with the descriptions of “Clinical trial use only”, “Keep out of the reach of children.” and “Caution: New Drug --Limited by United States law to investigational use” as well as other required information according to the local regulatory requirements in the local language.

5.5 IP Retrieval and/or Destruction

Used and unused study drug should be returned to the sponsor for destruction unless prohibited by site policy. In this instance, study drug may be destroyed at the study center according to standard institutional procedures after verification for drug accountability has been conducted by the study monitor, Sponsor or representative. Should this occur, a copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor. Upon destruction, a copy of the certificate of destruction must be provided for the Sponsor files and site drug accountability records.

5.6 Dose Dispensing and Assessment of Compliance

Volunteer’s compliance will be assessed by the following formula:

$$\frac{\text{\# of sachets of study drug actually administered}}{\text{Total \# of sachets of study drug assigned at that level}} \times 100\%$$

6. STUDY MEASUREMENTS

6.1 Eligibility

Eligibility should be thoroughly checked by the investigators at Screening visit and Day 1 visit.

If a volunteer is a screen failure, a minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the regulatory authority requirement and to respond to queries from regulatory authorities and IRBs/IECs. Minimal information includes demographics, screen failure details, concomitant medication, and any serious adverse event.

Re-screening for volunteer's eligibility will be allowed if the volunteer is willing to participate in the study and one of the following conditions meets:

- If a volunteer consents to participate and meets the eligibility criteria but a delay occurs in starting to participate in due to certain change in situation such that some measurement relevant to eligibility became invalid owing to the delay
- If the cause of screen failure has now resolved or adequately treated such that volunteer's conditions have now stabilized
- If there is an alternative manner to indicate that the volunteer may be suitable.

In these situations,

- A new eCRF will be used
- A new Screening number will be assigned to the person
- The person will be marked as having been re-screened on both the eCRF and the source document.
- The old eCRF will be completed as fully as possible following eCRF completion guide and data on the old eCRF is not copied to the new eCRF.
- The volunteer needs to sign a new ICF as part of the screening procedure.

It is not appropriate to re-screen a volunteer if he/she has previously failed to meet the eligibility criteria and no further changes or treatments have been able to indicate that the volunteer may be suitable.

Volunteer may be re-tested/measured for procedures relevant to causes of screen failure if investigator considers such causes can be resolved soon.

6.2 Medical History

General medical history within 6 months should be recorded at Screening visit. Histories of psychiatric disorder, left ventricular outflow obstruction, HIV infection or hepatitis B or C, and major surgery will be recorded on a lifetime basis.

6.3 Medication History

Previous medications should only be recorded up to 4 weeks before Screening visit.

6.4 Demographics, Physical Examination, Vital Signs, Height, and Body Weight

Demographics including gender, date of birth, and race will be collected at Screening visit.

Physical examination conducted in this study will include the following items: general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other.

Vital signs measurement will consist of systolic/diastolic blood pressure, respiratory rate, pulse rate or heart rate, and body temperature. Respiratory rate, pulse rate or heart rate and blood pressure (systolic/diastolic) will be obtained after the volunteer has been at rest for at least 5 minutes in a sitting position.

Height will be recorded only at Screening visit. Body weight will be recorded at all scheduled visits except visit 8 and 9.

Healthy volunteers should come fasted, specific for pre-dose measurement of physical examination, vital signs, and body weight prior to Careseng 1370 administration during dosing period (Day 1 to Day 5).

6.5 Laboratory Examination and PK sampling

Laboratory examination to be measured in this study will consist of the following:

Hematology: hemoglobin, hematocrit (Hct), RBC, WBC (with differential), absolute neutrophil count (ANC), lymphocyte count, platelets, international normalized ratio (INR) of prothrombin time (PT), activated partial thromboplastin time (APTT).

Immunology: CD3, CD4, CD8, CD19, CD16 and CD56 assessments, presented as CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD16+/CD56+, and CD4/CD8 ratio.

Biochemistry: AST, ALT, albumin, alkaline phosphatase (ALP), total bilirubin, creatinine, blood urea nitrogen (BUN), c-reactive protein, total protein, gamma glutamyl transferase (γ-GT), blood glucose, uric acid, total cholesterol, triglycerides, sodium, potassium, calcium, magnesium, phosphorus, amylase, lipase.

Urinalysis: pH, protein, RBC, WBC, casts.

Healthy volunteers should come fasted for laboratory examinations at all scheduled time points, except 8 hours post-first dose on Day 1, and 4 hours post-dose on Day 5.

The definition of "pre-dose PK blood sampling" means blood collection for PK prior to the first dose of that day (level A-D), or at scheduled visits without dosing of that day (level D). The definition of "post-dose" means the PK blood sampling after the 1st dose on Day 5. PK blood samplings at scheduled time points will be collected and examined for the concentration of 20(S)-protopanaxadiol (PPD) and its metabolites, and analyzed for PK parameters.

6.6 Dosing, Dispense and Retrieve Careseng 1370

Careseng 1370 will be dosed at site and dispensed for taking at home following the table below. Used and unused IP will be returned at the next scheduled visits.

	Day 1	Day 2	Day 3	Day 4	Day 5
Breakfast	Site	Site[#]	Site	Site[#]	Site
Lunch[*]	Site	Home	Home	Home	Site

*[#]Not required for level D; *Not required for level A and D*

Volunteers should take Careseng 1370 for lunch (if there is one) at 4 hours (+ 10 minutes) after taking Careseng 1370 for breakfast on that day. The definition of "dosing at home for lunch" means that subjects leave the site and administer the second dosing somewhere else before lunch except level A and D (off-site dosing).

6.7 12-Lead EKG and Chest X-Ray

12-Lead EKG measurement will at least include rhythm, ventricular rate, PR interval, QRS duration, QT and QTc intervals. Healthy volunteers should come fasted, specific for pre-dose measurement of 12-Lead EKG prior to Careseng 1370 administration during dosing period (Day 1 to Day 5).

Chest X-Ray will only be performed at Screening visit and per investigator's discretion for unscheduled visit if necessary.

6.8 Dispense and Retrieve Diary

The information to be collected in diary should contain at least number of sachets taken at home of Day 2 to Day 4 and each dosing time.

6.9 Pregnancy Test

Volunteer's pregnancy status should be checked by serum or urine pregnancy test at Screening and Final visit and any time if investigator or volunteer suspects the volunteer is pregnant.

7. STUDY SCHEDULE

In traditional 3+3 paradigm settings, eligible volunteers will be assigned to one of the candidate dose cohorts. The starting dose of the dose escalation scheme begins from

level A.

The schedule of assessment is tabulated in front of the protocol main text. The assessments or procedures to be performed at each study visit are listed below. The results of protocol specific assessments and procedures will be recorded in the source documents for all study volunteers and on the appropriate page of the eCRF.
Unscheduled visit will be arranged when investigator considers necessary.
Healthy volunteers should come fasted for all scheduled visits except visit 8, and 9.
The definition of "pre-dose" means the timing prior to the 1st dose of that day (level A-D), or the timing for examinations scheduled on that day (2nd and 4th days of level D).
The definition of "post-dose" means the timing after the 1st dose on Day 5. The duration of dosing time between breakfast and lunch from Day 2 to Day 5 should be as close to those for Day 1. Volunteers should take Careseng 1370 for lunch (if there is one) at 4 hours (+ 10 minutes) after taking Careseng 1370 for breakfast on that day. Similarly, time points for pre-dose PK blood sampling on Day 2 to Day 5 should be as close as that on Day 1.

Screening (Days -14 to -1; Visit 1)

- Obtain informed consent form
- Assign volunteer identifier
- Obtain medical history
- Collect volunteer demographics data
- Record medication history (including concomitant medications)
- Measure height
- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG (test performed within 14 days are acceptable)
- Perform pregnancy (urine or serum test for female volunteers of childbearing potential)
- Conduct laboratory tests (with immunology test) (test performed within 14 days are acceptable) (fasting)
- Conduct chest X-ray (test performed within 14 days are acceptable)
- Assess the volunteer's eligibility for the study (inclusion/exclusion criteria)
- Record adverse events
- Dispense diary

1st Hospitalization (Day -1 to Day 1; Visit 2)

Day -1

Registration for hospitalization in the evening

Day 1

Pre-dose (fasting)

- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG
- Pre-dose PK blood sampling
- Diary return and dispensing
- Assess the volunteer's eligibility for the study (inclusion/exclusion criteria)

During the treatment

- Dosing before breakfast at site
- Perform physical examination (8 hours post-first dose, ±20 minutes are allowed)
- Assess vital signs (1, 4 and 8 hours post-first dose, ±20 minutes are allowed)
- Conduct 12-lead EKG (1, 4, 8, and 12 hours post-first dose, ±20 minutes are allowed)
- Conduct laboratory tests (excluding immunology test, only for 8 hours post-first dose, ±20 minutes are allowed)
- Dosing before lunch at site (not applicable for Dose level A and D)
- Record adverse events
- Record concomitant medications

1st Discharge (Day 2; Visit 3)

Pre-dose (fasting)

- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG
- Conduct laboratory tests (with immunology test) together with pre-dose PK blood sampling

During the treatment

- Dosing (if scheduled) before breakfast at study site

Post-dose

- Conduct 12-lead EKG about 1 hour after IP administration (except level D)
- Record adverse events
- Record concomitant medications
- Drug (except level A and D) dispensing, and diary return and dispensing

Dosing Visits (Days 3 and 4; Visits 4 and 5)

Pre-dose (fasting)

- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG
- Conduct laboratory tests (except immunology test) together with PK blood sampling
- Drug (except level A and D) and diary return

During the treatment

- Dosing (if scheduled) for breakfast at site

Post-dose

- Conduct 12-lead EKG about 1 hour after IP administration (except level D on Day 4)
- Record adverse events
- Record concomitant medications
- Drug (except level A and D) and diary dispensing

2nd Hospitalization (Day 4 to Day 5; Visit 6)

Day 4

Registration for hospitalization after planned dosing (if scheduled) on Day 4

Note: This implementation aims to perform the planned procedures at the similar timing as those on Day 1.

Day 5

Pre-dose (fasting)

- Measure body weight
- Perform physical examination
- Assess vital signs

- Conduct 12-lead EKG
- Conduct laboratory tests (except immunology test) together with PK blood sampling
- Drug (except level A and D) return, and diary return and dispensing

During the treatment

- Dosing before breakfast at site (last dose for level A and D)
- Dosing before lunch at site (not applicable for Dose level A and D; last dose for level B and C)

Post-dose PK blood sampling

- Dose level A and D: post-dose PK blood sampling at 0.5 hour (± 5 minutes), 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 5 minutes), 12 hours (± 20 minutes), 24 (± 2) hours (at Visit 7), 48 (± 2) hours (at Visit 8), and 72 (± 2) hours (at Visit 9)
- Dose level B and C: post-dose PK blood sampling at 0.5 hour (± 5 minutes), 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 5 minutes), 4.5 hours (± 5 minutes), 5 hours (± 5 minutes), 6 hours (± 5 minutes), 7 hours (± 5 minutes), 8 hours (± 5 minutes), 9 hours (± 5 minutes), 10 hours (± 5 minutes), 12 hours (± 20 minutes), 16 hours (± 20 minutes), 24 (± 2) hours (at Visit 7), 48 (± 2) hours (at Visit 8), and 72 (± 2) hours (at Visit 9)
- Conduct laboratory tests (except immunology test) (only for 4 hours post-dose, ±20 minutes are allowed)
- Perform physical examination (only for 4 hours post-dose, ±20 minutes are allowed)
- Assess vital signs (only for 4 hours post-dose, ±20 minutes are allowed)
- Conduct 12-lead EKG (only for 1, 4, 8, and 12 hours post-dose, ±20 minutes are allowed)
- Record adverse events
- Record concomitant medications

2nd Discharge (Day 6, 24 (± 2) hours post-dose; Visit 7)

- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG
- Conduct laboratory tests (with immunology test) together with PK blood sampling for 24 (± 2) hours post-dose (fasting)
- Record adverse events

- Record concomitant medications
- Diary return and dispensing

Follow-up Visit (Day 7, 48 (± 2) hours post-dose; Visit 8)

- PK blood sampling for 48 (± 2) hours post-dose
- Diary return
- Record adverse events
- Record concomitant medications

Follow-up Visit (Day 8, 72 (± 2) hours post-dose; Visit 9)

- PK blood sampling for 72 (± 2) hours post-dose
- Record adverse events
- Record concomitant medications

Follow-up Visit (Day 12 ± 2; Visit 10)

- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG
- Conduct laboratory tests (except immunology test) (fasting)
- Record adverse events
- Record concomitant medications

Final Visit (Day 22 ± 2; Visit 11, or within 3 days after withdrawal)

- Measure body weight
- Perform physical examination
- Assess vital signs
- Conduct 12-lead EKG
- Perform pregnancy test for female volunteers of childbearing potential
- Conduct laboratory tests (with immunology test) (fasting)
- Record adverse events
- Record concomitant medications

Un-scheduled visit

Items performed should be per investigator's decision except the following:

- Record adverse events
- Record concomitant medications

8. ADVERSE EVENTS

8.1 Definitions

- **Adverse Event (AE):**

  An AE is any untoward medical occurrence in a volunteer or clinical investigation participant administered a study medication and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study medication, whether or not related to the study medication. Laboratory abnormalities should not be recorded as AEs unless determined to be clinically significant by the Investigator.

- **Expected AE:**

  Expected AE is defined as any event, the specificity or severity of which is consistent with the current investigator brochure or other technique documents.

- **Unexpected AE:**

  Unexpected AE is defined as any event, the specificity or severity of which is not consistent with the current investigator brochure or other technique documents. "Unexpected", as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

- **Serious Adverse Event (SAE):**

  Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following conditions:

  - Death during the period of protocol defined surveillance
  - Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
  - An event requiring in volunteer hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
  - Results in congenital anomaly or birth defect
  - Results in a persistent or significant disability/incapacity

- Based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2 AE/SAE Intensity and Relationship Assignment

- **AE/SAE Intensity**

The investigator must rate the intensity for all AEs that occur during the study, following "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[12] (Appendix 1), issued by United States Food and Drug Administration in September 2007. The definition of Grade 5 (death) was added to this grading system as it was not defined in the guidance.

The toxicity grade of adverse events will be rated according to the following definition by the investigator when AEs are not listed in the US FDA Guidance (Appendix 1) applied in this study:

- Grade 1 (Mild):
  No interference with activity
- Grade 2 (Moderate):
  Some interference with activity not requiring medical intervention
- Grade 3 (Severe):
  Prevents daily activity and requires medical intervention
- Grade 4 (Life threatening):
  Emergency room visit or hospitalization
- Grade 5 (Death)

Note: The definitions of Grade 1 to Grade 4 follow "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[12] issued by United States Food and Drug Administration in September 2007 (Appendix 1). The definition of Grade 5 (death) was added to this grading system as it was not defined in the guidance (Section 8.2 and Appendix 1).

- **AE/SAE Relationship Assessment**

The investigator will be asked to assess all AEs with respect to their causal relationship to the study drug according to the following classification:

- Definitely Related

  There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study agent/intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study agent/intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related

  There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study agent/intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possibly Related

  There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the volunteer's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.

- Unlikely

  A clinical event, including an abnormal laboratory test result, whose temporal relationship to study agent/intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the volunteer's clinical condition, other concomitant treatments).

- Not related

  The AE is completely independent of study agent/intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician
  Expected Events Related to Disease Process: Provide explicit definitions of the

type(s), grade(s), and duration(s) of adverse event(s) that will be considered disease related.

8.3 Collecting, Recording and Reporting of Adverse Events

8.3.1 Collecting and Reporting of AE

AEs may be volunteered spontaneously by the study volunteer, discovered as a result of general questioning by the study staff, or determined by physical examination. All AEs will be recorded on the eCRF. For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE, even after the date of study drug discontinuation, is required if the AE persists. The study volunteer will be followed until the event resolves or stabilizes at a level acceptable to the investigator.

8.3.2 Reporting of AE

Serious, alarming and/or unusual adverse events must be reported to the Sponsor/CRO contact within 24 hours of the investigator's knowledge of the event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a volunteer’s participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the eCRF)

The investigator is responsible to communicate details of medical emergencies in trial volunteers to the Ethics Committee. Sponsor is responsible to inform the events to the regulatory authorities.

Fatal or life-threatening, unexpected ADRs should be notified to Taiwan National ADR Reporting Center by sponsor/CRO as soon as possible, but no later than 7 calendar days and a complete report should be followed 8 additional calendar days. This report must include an assessment of the importance and implication of the findings and/or previous experience on the same or similar medical products. Serious, unexpected ADRs that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days.

Adverse events observed during the study will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by System/Organ/Class classified in MedDRA as appropriate. The toxicity grade of adverse events will be rated according to "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[12] defined in Section 8.2 and Appendix 1.

The version of MedDRA employed will be agreed by the sponsor and remains unchanged throughout the study.

9. DATA ANALYSIS

9.1 Data Quality Assurance

Electronic CRFs will be provided for the recording and collection of volunteer data. All eCRFs will be completed following eCRF completion guide after the volunteer's visit. Corrections to data on the eCRFs will be documented or traced. The investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the investigator will need to again sign the investigator signature page. Designated source documents will be signed and dated by the appropriate study personnel.

9.2 Clinical Data Management

The investigator must agree to complete and maintain source documents and eCRFs for each volunteer participating in the study or by his/her designees.

The sponsor/CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the sponsor/CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines and the sponsor/CRO's SOPs as well as provisions of the study-specific data management plan.

10. SAMPLE SIZE AND STATISTICAL METHODS

10.1 Determination of Sample Size

Planned 4 cohorts of up to 6 evaluable healthy volunteers in design of traditional 3+3 paradigm with three candidate dose levels, the number of evaluable healthy volunteers will be up to 24. Around 29 eligible healthy volunteers will be recruited to complete up to 24 evaluable healthy volunteers.

Note: A volunteer is considered evaluable if he/she

1. receives any Careseng 1370, and

2. experiences DLT OR completes DLT observation period with at least 80% of study drug compliance and has exposed to Careseng 1370 for at least 4 days (level A, B and C), OR completes DLT observation period with 100% of study drug compliance (level D).

10.2 Statistical and Analytical Plans

10.2.1 Analysis Population

The following populations are defined for statistical analysis.

Intent-to-treat (ITT) population:
– Volunteers receive any Careseng 1370

Demographic analysis, safety evaluation and pharmacokinetic analysis will be performed on the ITT population. Decision of the MTD will be made based on DLT observation of evaluable subjects.

10.2.2 Statistical analysis

Baseline characteristics, including demographic data such as gender, age, etc., will be presented using descriptive statistics and displayed by dose level (levels A to D). Additionally, descriptive statistics will be provided for all of the endpoints by dose level. Frequency table will be provided for categorical data, while mean, standard deviation, maximum, minimum, median, inter-quartile range (IQR), and 95% two-sided confidence interval (for data change from baseline) will be calculated for continuous measurements.

Safety Analyses
Adverse events observed after signing informed consent form till exit from study will be coded using Medical Dictionary for Regulatory Activities (MedDRA) using the version agreed by sponsor and will be reported by dose level by System/Organ/Class and Preferred Terms classified in MedDRA as appropriate. The toxicity grade of adverse events will be rated according to definition in Section 8.2. Findings in physical examinations will be displayed

for each individual system. Changes from pre-dosing laboratory test results, body weight, EKG and vital signs to applicable post-dosing visits will be analyzed by descriptive statistics and (if applicable) will be presented by transition table for normality (normal, clinically not significant, clinically significant). Findings in 12-Lead EKG and X-ray will be presented by description.

10.2.3 Interim Analyses

There is no planned interim analysis for this study.

10.2.4 Missing Data

Missing data will be treated as missing. No missing data imputation will be employed.

11. ETHICAL CONSIDERATIONS

11.1 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families.

Consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.2 IRB and Regulatory Review

This protocol and the associated informed consent documents must be submitted to the IRB and health authority for review and approval. The study will not be initiated until the IRB and health authority provide written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and sponsor or CRO.

No changes from the final approved protocol will be initiated without the health authority's and IRB/EC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the study participants or when the change involves only logistics or administration. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation, and will be addressed as such during the reporting of the study.

11.3 Confidentiality of Data and Volunteer Records

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating volunteers.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The information provided by sponsor in this protocol and the associated Clinical Investigator's Brochure and the data generated by this clinical study are to be considered as confidential property of sponsor.

11.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

12. PUBLICATIONS

The data and information associated with this study may be used by sponsor now and in the future for the purposes of presentation, publication at discretion of sponsor or for submission to regulatory authority. In addition, relative to the release of any proprietary information, sponsor reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the investigator agrees to the release of the data from this study and acknowledges the above publication policy.

13. RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation should be retained by the PI in a secure storage facility. The records should be accessible for inspection and copying by authorized authorities.

All study documentation at the clinical site and sponsor records will be archived in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), applicable regulations, the sponsor's quality standards and Standard Operation Procedures (SOP)s. Study records should not be destroyed without prior written agreement between sponsor or CRO and the study investigator.

14. PROTOCOL AMENDMENT HISTORY

The major amendments in protocols up to current version are provided in the following table.

Version	Date	Description of Major Changes	Brief Rationale
1.0	14SEP2018	NA	NA
1.1	24JAN2019	Add PK blood sampling	To explore PK profiles of marker ingredient
		Add 24-hour 12-Lead EKG monitoring	To ensure safety of volunteers
		Add laboratory test items: aPTT, PT, and INR	To ensure safety of volunteers
		Change dosing period from 21 days to 5 days	Five days for collecting safety profiles in healthy volunteers are sufficient
		Correct definition of severity of AE	Original definition is not for healthy volunteers
1.2	21MAY2019	Adjust PK sampling time points and revise the schedule of assessments	Based on the PK profile of marker ingredient, PPD
		Extend the safety follow-up period, and add follow-up visits at Day 15 and Day 22 to monitor the long term safety	Per TFDA's comment
		Staggering time between first 3 subjects is changed to 5 days	Per TFDA's comment
		Prohibit herbal supplement and medicinal food to avoid interfering PK analysis	Per TFDA's comment
		Extend the wash-out period to 2 weeks in Exclusion Criterion 3	Per TFDA's comment
		Add exclusion criterion 14: Plan to receive surgery from the Screening visit until the Final visit	To avoid subject receiving surgery during the trial for safety concerns
2.0	10JUL2019	Duration for observing DLT changed back to within 9 days after Day 1	Per TFDA's comment
		Delete Dose Level D (4 sachets), and adjust number of volunteers to enroll	To avoid Fujicalin ($CaHPO_4$) overdose
		Add 0.5 and 72 hour (on Day 8) PK sampling time points	To expand range of PK time points
		Prohibit phosphorous supplement, calcium supplement, or food rich in calcium during the study, and avoid food very rich in phosphorous	To avoid Ca or P overdose
		Add exclusion criterion 15: Known or suspected hypersensitivity to any component of Careseng 1370, including components in plants of genus *Panax*, Tween 80, Kolliphor® P188, Fujicalin, and ginseng flavor	Per CDE consultation
		Add section for conflict of interests	For ethical concerns
		Prohibited therapy will not lead to being excluded from PP population or withdrawal	For statistical concerns

Version	Date	Description of Major Changes	Brief Rationale
2.1	08NOV2019	Increase EKG exam frequency on Day 1 and 5	Per TFDA's comment
		Alteration of the principle investigator and the corresponding information.	Request by the sponsor
		One night extension of planned hospitalization	
3.0	08APR2020	Change of DLT observation period as Day 1 to Day 10	Request by the DSMB to clarify the definition of DLT
		Revision of the definition for MTD	Typo to be corrected
		Addition of special scenarios in dose escalation/de-escalation scheme for DSMB review	Granted by the DSMB
		Clarification for the definition of evaluable subjects	Request by the DSMB
		Requirement of fasting on Visit 7	For the requirement of lab tests
		Additional immunology test on Day 2 and Day 22	Request by the sponsor
		Additional cytokines included for immunology test: CD16 and CD56	Request by the DSMB
		Revision of withdrawal criteria # 7 for study drug compliance	Request by the DSMB to be consistent with the study drug compliance
		Revision of the schedule for Visit 10 as Day 12 (± 2)	Request by the DSMB to clarify the DLT observation period
		Revision of concomitant therapy # 5: redefinition of food restriction in high calcium and provision of a calcium-restricted diet plan	Request by the DSMB to re-define the restriction for low-calcium diet
4.0	10AUG2020	Definition of pre-dose and post-dose for this study	Clarification of time points for PK blood sampling
		Re-definition of PK blood sampling time points and additional time points for PK blood sampling of Dose level B and C	Requested by the sponsor for PK analysis
		Additional description to clarify which measurements require fasting	Clear statement for fasting required measurements
5.0	18SEP2020	Addition of 1 lower dose cohort (level D), and the corresponding information	Consideration of unexpected drug effects on human body for safety
		Re-definition of pre-dose and pre-dose PK blood sampling	Corresponding change in response to the addition of 1 lower dose cohort (level D)
		Addition of detailed information for results of immunology	Clear statement for the presentation of immunology results

15. REFERENCES

1. Wen J., Zimmer E.A., Phylogeny and biogeography of Panax L. (the Ginseng genus, Araliaceae): inferences from its sequences of nuclear ribosomal DNA Mol. Phylogenetics Evol. 1996;167-177

2. Li D., Cao J., Bi X., Xia X., Li W., Zhao Y., New dammarane-type triterpenoids from the leaves of Panax notoginseng and their protein tyrosine phosphatase 1B inhibitory activity J Ginseng Res. 2014 Jan; 38(1): 28–33.

3. Guo H.B., Cui X.M., An N., Cai G.P., Sanchi ginseng (Panax notoginseng (Burk.) F.H. Chen) in China: distribution, cultivation and variations Genet. Resour. Crop Evol., 2010;57, 453-460.

4. Committee for the pharmacopoeia of China Pharmacopoeia of China, Part I, China Medical Science And Technology Press., Beijing (2010).

5. Sun S., Wang C.Z., Tong R., Li X.L., Fishbein A., Wang Q., He T.C., Du W., Yuan C.S., Effects of steaming the root of *Panax notoginseng* on chemical composition and anticancer activities Food Chem., 2010;118:307-314.

6. Zhao G.R., Xiang Z.J., Ye T.X., Yuan Y.J.,.Guo Z.X Antioxidant activities of Salvia miltiorrhiza and *Panax notoginseng* Food Chem., 2006:99; 767-774.

7. Shi, J.P., Lu, J.Z., Liu, R.X., Guo, J.W., Deng, Z.J., Li, L.M.,. Analysis on dosage form and technology of Chinese patent medicine containing *Panax notoginseng* in Chinese pharmacopoeia (2010 edition). Pharmacy Today 2012; 22:392–394.

8. Jiang B.H., Zhao Y. Q., Sun J.J., Zhao Y., Hu X.M., Liu L. Enzymatic transformation of Panax notoginseng stem and leaves for preparation anti-tumor activity constituents BTAIJ, 10(5), 2014;1066-1073.

9. Wang R.F., Li J. Hu H.J., Li J. Yang Y.B., Yang L., Wang Z.T. Chemical transformation and target preparation of saponins in stems and leaves of Panax notoginseng. J Ginseng Res (2016) 1-7.

10. Wang C.Z., Luo X.J., Zhang B., Song W.X., Ni M., Mehendale S., Xie J.T., Aung H.H., He T.C., Yuan C.S., Notoginseng enhances anti-cancer effect of 5-fluorouracil on human colorectal cancer cells. Cancer Chemother Pharmacol. 2007;60(1):69-79.

11. Study Report. Drug Development of DS1370 on Myelosuppression Attenuation that Induced by Chemotherapy II. Institute of Pharmaceutics, Natural Resource Development, Development Center for Biotechnology, Taiwan. Study No.:CBC0606102; Report Date: Oct 31, 2017.

12. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. United States Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. September 2007. (**Appendix 1**)

16. APPENDIX

Appendix 1

Guidance for Industry
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials