

## CLINICAL STUDY PROTOCOL

### **A Phase 1 Randomized, Double Blinded, Placebo-Controlled Single Dose Escalation Study of OsrHSA in Adult Healthy Male and Female Volunteers**

This study will be conducted according to this protocol, including protocol amendments and in compliance with Good Clinical Practice, the ethical principles, and other applicable regulatory requirements.

<b>Protocol Number:</b>	US-HY1001
<b>Clinical Phase:</b>	Phase I
<b>IND Number:</b>	19136
<b>Sponsor:</b>	Wuhan Healthgen Biotechnology Corporation
<b>Version:</b>	V 1.2
<b>Version Date:</b>	11/20/2019

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## **SPONSOR SIGNATURE**

### **Study Title:**

A Phase 1 randomized, double blinded, placebo-controlled single dose escalation study of OsrHSA in adult healthy male and female volunteers

**Protocol Number:** US-HY1001

**Version:** 1.2

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor,  
Qinhui Song MD, PhD \_\_\_\_\_

Signature by:

\_\_\_\_\_  
Date: November 20, 2019



## INVESTIGATOR AGREEMENT

I have read Protocol “A Phase 1 randomized, double blinded, placebo-controlled single dose escalation study of OsrHSA in adult healthy male and female volunteers” and agree to conduct the study as described therein in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

The signature below constitutes my agreement to the contents of this protocol (version 1.2, date November 20, 2019).

---

*Signature*

*Date*

---

*Name (please type or print)*

David Nguyen, MD

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<b>AE</b>	Adverse Event
<b>ALP</b>	Alkaline Phosphatase
<b>ALT</b>	Alanine Transaminase
<b>ANC</b>	Absolute number of neutrophils
<b>aPTT</b>	Activated Partial Thromboplastin Time
<b>AST</b>	Aspartate Transaminase
<b>AUC</b>	Area Under the Curve
<b>BP</b>	Blood Pressure
<b>BUN</b>	Blood Urea Nitrogen
<b>CBC</b>	Complete Blood Count
<b>CMP</b>	Comprehensive Metabolic Panel
<b>CNS</b>	Central Nervous System
<b>ConMeds</b>	Concomitant medications
<b>CRF (eCRF)</b>	Case Report Form (Electronic Case Report Form)
<b>CRO</b>	Contract Research Organization
<b>CSR</b>	Clinical study report
<b>CT</b>	Computed Tomography
<b>DLT</b>	Dose Limiting Toxicity
<b>DNA</b>	Deoxyribonucleic acid
<b>DP</b>	Drug Product
<b>ECG</b>	Electrocardiogram
<b>ECOG</b>	Eastern Cooperative Oncology Group
<b>EDC</b>	Electronic Data Capture
<b>EOS</b>	End-of-Study
<b>EOT</b>	End of Treatment
<b>FDA</b>	Food and Drug Administration
<b>GCP</b>	Good Clinical Practice
<b>G-CSF</b>	Granulocyte Colony-Stimulating Factor
<b>GI</b>	Gastrointestinal
<b>GLP</b>	Good Laboratory Practice

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<b>GMP</b>	Good Manufacturing Practice
<b>H1</b>	Histamine-1
<b>HbcAb</b>	Hepatitis B core antibody
<b>HBsAg</b>	Hepatitis B Surface antigen
<b>HBV</b>	Hepatitis B virus
<b>HCV</b>	Hepatitis C virus
<b>HIV</b>	Human immunodeficiency virus
<b>HNSTD</b>	Highest noseverely toxic dose
<b>HR</b>	Heart rate
<b>IB</b>	Investigator's Brochure
<b>IBD</b>	Inflammatory Bowel Disease
<b>IC50</b>	Half maximal inhibitory concentration
<b>ICF</b>	Informed Consent Form
<b>ICH</b>	International Conference on Harmonization
<b>IEC</b>	Independent Ethics Committee
<b>IgG</b>	Immunoglobulin G
<b>INR</b>	International Normalized Ratio
<b>IRB</b>	Institutional Review Board
<b>IRR</b>	Infusion Related Reaction
<b>IUD</b>	intrauterine device
<b>IUS</b>	Intrauterine system
<b>IV</b>	Intravenously
<b>IVIG</b>	IV immunoglobulin
<b>MCH</b>	Mean Corpuscular Hemoglobin
<b>MCHC</b>	Mean Corpuscular Hemoglobin Concentration
<b>MCSF</b>	Macrophage Colony-Stimulating Factor
<b>MCV</b>	Mean Corpuscular Volume
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>MRI</b>	Magnetic Resonance Imaging
<b>MRSD</b>	Maximum Recommended Starting Dose
<b>Nabs</b>	Neutralizing antibodies

<b>NYHA</b>	New York Heart Association
<b>PDF</b>	Portable Document Format
<b>PDX</b>	Patient derived xenograft
<b>PE</b>	Physical examination
<b>PET</b>	Positron emission therapy
<b>PK</b>	Pharmacokinetics
<b>PT</b>	Prothrombin time
<b>QA</b>	Quality assurance
<b>QC</b>	Quality control
<b>QTcF</b>	QT-interval corrected according to Fridericia's formula
<b>RBC</b>	Red blood cells
<b>RDW</b>	Red Cell Distribution Width
<b>REB</b>	Research Ethics Board
<b>RNA</b>	Ribonucleic acid
<b>SAE</b>	Serious Adverse Event
<b>SMP</b>	Study Monitoring Plan
<b>SOC</b>	System organ class
<b>SOP</b>	Standard Operating Procedures
<b>SPR</b>	Surface plasma resonance
<b>SRC</b>	Safety Review Committee
<b>SUSARs</b>	Suspected Unexpected Serious Adverse Reactions
<b>TCR</b>	Tissue cross-reactivity
<b>TEAE</b>	Treatment Emergent Adverse Event
<b>TK</b>	Toxicokinetics
<b>ULN</b>	Upper Limit of Normal
<b>UPCR</b>	Urine Protein to Creatinine Ratio
<b>WBC</b>	White Blood Cells

## 1 PROTOCOL SUMMARIES

### 1.1 Synopsis

<b>Title:</b>	A Phase 1 randomized, double blinded, placebo-controlled single dose escalation study of OsrHSA in adult healthy male and female volunteers
<b>Sponsor:</b>	Wuhan Healthgen Biotechnology Corporation
<b>Study Drug:</b>	OsrHSA (Recombinant Human Albumin from <i>Oryza sativa</i> ) for infusion  Normal Saline (0.9% Sodium Chloride) will be used as the placebo
<b>Clinical Trial Phase:</b>	Phase 1
<b>Proposed Indication:</b>	Circulatory dysfunction due to hypovolemia, including patients with cirrhotic ascites and hypoalbuminemia
<b>Primary Objectives:</b>	<ul style="list-style-type: none"><li>To assess the safety and tolerability profile of OsrHSA when administered as single dose IV infusion</li></ul>
<b>Secondary Objectives:</b>	<ul style="list-style-type: none"><li>To characterize the pharmacokinetics (PK) of OsrHSA when administered as single dose IV infusion</li><li>immunogenicity profiles of OsrHSA when administered as single dose IV infusion</li></ul>
<b>Exploratory</b>	To assess changes in serum albumin level, colloid osmotic pressure, blood pressure and body weight when

<b>Objectives:</b>	administered as single dose IV infusion
<b>Study Population:</b>	Healthy male and female volunteers, non-smokers, 18-55 years of age
<b>Number of Subjects planned:</b>	Up to 40 subjects, additional subjects might be recruited depending on emerging data from current study and the ongoing trial in China
<b>Number of Study Centers Planned:</b>	One study site located in the United States
<b>Study Design:</b>	<p>This is a Phase 1 randomized, double blinded, placebo-controlled, single dose escalation study to evaluate safety, tolerability, PK, and immunogenicity of OsrHSA in healthy volunteers (See <a href="#">study design schema</a>).</p> <p>After a screening period of up to 28 days, the qualified subjects will be randomized to OsrHSA or placebo (6:2). Each enrolled subject will receive one single assigned dose of OsrHSA or placebo. The investigator and subjects will be blinded to treatment assignment. During the study, subjects will be evaluated for safety and tolerability, PK/PD, and activity of OsrHSA.</p> <p>On day 1, OsrHSA or placebo will be administered as single IV infusion at a rate lower than 2 ml/min to the subjects. Patients will be observed overnight. On Day 2, after completion of the study procedures and assessments, subjects will be discharged from the clinical research center. Seven-day dose-limiting toxicity (DLT) observational period will commence upon completion of dosing at the end of infusion (EOI). Subjects will have end-of-study (EOS) follow-up visits on Day 30 after infusion.</p> <p>The planned doses are 20, 40, 80, 140, and 200 mg/kg, dose level(s) higher than 200mg/kg might be an option(s) based on emerging data from this study and ongoing China clinical trial (China IND#: CXSL1500135; Protocol Number: HY1001) .</p>

Dose escalation decisions will be determined based on toxicities data as well as available all available PK data observed within 7 days after dosing.

**Study participation  
Duration:**

The screening period is up to 28 days, one treatment day, and follow-up period of 30 days

**Pharmacokinetic (PK)  
evaluations:**

Blood samples for single dose PK will be collected from all subjects to determine the albumin concentration changes, they will be taken at time points listed in [Table 1](#). The PK of OsrHSA will be analyzed using standard non-compartmental analysis (NCA) by validated software WinNonLin version 6.4 or higher (Certara, NJ, USA). PK parameters derived from NCA analysis will include, but not limit to,  $AUC_{0-\infty}$  and  $AUC_{0-t}$ ,  $C_{max}$ ,  $t_{1/2}$ , CL, and  $V_d$ . PK parameters will be listed for each subject and summarized with descriptive statistics by each dose level/cohort. PK parameters will also be presented with baseline corrected.

Blood samples for immunogenicity will be collected at time points shown in [Table 1](#). Neutralization activity will be evaluated if ADA is positive.

**Safety Evaluations:**

The safety population will consist of all subjects who are infused the study drug and have at least one post-dose safety assessment. Safety will be assessed by physical examinations, vital signs, electrocardiograms, AEs monitoring. AEs are graded per Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*.

**Efficacy Evaluations:**

The parameters including, but not limited to, serum albumin level, colloid osmotic pressure, blood pressure, 24-hour fluid input and urine output, and body weight will be measured at baseline and at time points listed in [Table 1](#). The changes in serum albumin level, colloid osmotic pressure, blood pressure, body weight and other parameters will be assessed.



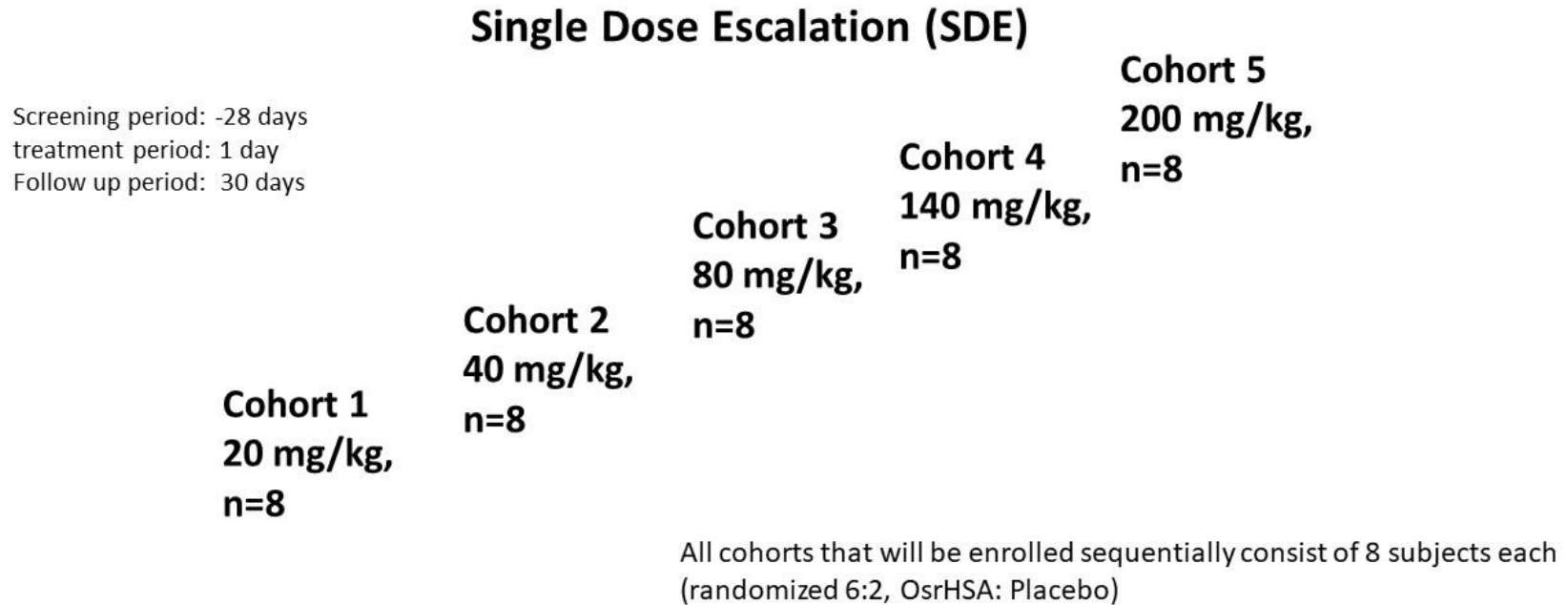
**Immunogenicity:** Blood samples for immunogenicity will be collected until 30 days after the infusion

**Statistical Analysis:** All PK, immunogenicity, safety and efficacy data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables.

## 1.2 Study Design Schema

Figure 1

### OsrHSA Phase 1 study design schema



### 1.3 Schedule of Activities

- a. Screening procedures will be performed at screening visits from D-28 to D-2, including ultrasound, smoking, alcohol, drug use test, serum albumin. Pre-dose from D-1 to infusion, smoking, alcohol, drug use test, serum albumin will be performed again. (The two times serum albumin average will be used as subject's baseline serum albumin)
- b. Urine collection will be performed 24hr after infusion
- c. The 0.5h time point after dose initiation will change to  $\pm 5$  minute window (instead of  $\pm 2$  minute).
- d. The D3 and D5 time points will change to  $\pm 6$  hour window (instead of  $\pm 4$ h)
- e. Abdominal ultrasound exam will be performed and reviewed during the 28 day screening period, prior to patient check-in on Day -1
- f. Alcohol and Cotinine will be tested at all follow-up visits (D3, D5, D8, D15, D22, D30)
- g. Syphilis will be tested at the screening timepoint, in order to adhere to the new exclusion criteria described above
- h. Anti-HCP antibody will be measured at the same time points as ADA
- i. In order to calculate accurate creatinine clearance, subjects' body weight will be re-measured at Day 8 and Day 30 visits.
- j.

Table 1 Schedule of Activities

Protocol Activity	Clinical Research Unit (CRU) Confinement										Outpatient Visits					
	Screen -D28 to -D2	Pre-dose -D1 to dose	Dose initiation	0.5 h $\pm$ 5m after Dose initiation	1.0h $\pm$ 10m after Dose initiation	EOI+ 10m	0.5h Post EOI $\pm$ 10m	4h $\pm$ 10m	12h $\pm$ 10m	D2 24h $\pm$ 30m	D3 $\pm$ 6h	D5 $\pm$ 6h	D8 $\pm$ 1d	D15 $\pm$ 2d	D22 $\pm$ 2d	D30 $\pm$ 2d
Signed Informed Consent (ICF) <sup>1</sup>	×															
Inclusion/Exclusion Criteria	×	×														

Protocol Activity	Clinical Research Unit (CRU) Confinement										Outpatient Visits					
	Screen -D28 to -D2	Pre-dose -D1 to dose	Dose initiation	0.5 h ± 5m after Dose initiation	1.0h ± 10m after Dose initiation	EOI+ 10m	0.5h Post EOI ± 10m	4h ± 10m	12h ± 10m	D2 24h ± 30m	D3 ± 6h	D5 ± 6h	D8 ± 1d	D15 ± 2d	D22 ± 2d	D30 ± 2d
Demographics <sup>2</sup>	×															
Weight <sup>3</sup>	×	×							×	×		×				×
Medical History <sup>4</sup>	×	×								×	×	×	×	×	×	×
Physical Examination <sup>5</sup>	×	×				×	×	×	×	×	×	×	×	×	×	×
Current Medications/OTC/supplements	×	×											×			×
Vital Signs <sup>6</sup>	×	×		×	×	×	×	×	×	×	×	×	×	×	×	×
12 Lead Electrocardiogram (ECG) <sup>7</sup>	×	×			×	×	×	×	×	×	×	×	×	×	×	×
Abdominal Ultrasound <sup>8</sup>	×															
Adverse Events (AE)	Ongoing															
Laboratory Tests																
Urine Drug Screen	×	×														
Alcohol Breath Test	×	×									×	×	×	×	×	×
Urine Cotinine Test	×	×									×	×	×	×	×	×
Pregnancy Test for Female <sup>9</sup>	×	×												×		×
Ig E and Ig G Against Rice	×							×			×	×		×		×
Hematology & Serum Chemistry <sup>10</sup>	×	×					×		×			×				×
Coagulation Tests	×											×				
Screening for HIV, HBV, HCV, Syphilis <sup>11</sup>	×															
Urine Analysis (U/A) <sup>12</sup>	×						×	×	×	×	×	×	×	×	×	×
Study Drug Administration			×													
Injection Site Reaction		×		×		×	×		×	×						
Pharmacokinetics (PK) <sup>13</sup>		×		×		×	×	×	×	×	×	×	×	×	×	×
Colloid Osmotic Pressure <sup>14</sup>		×		×		×	×	×	×	×	×	×	×	×	×	×
Anti-Drug Antibodies (ADA); Anti-HCP antibody <sup>15</sup>		×										×	×	×	×	×

**Abbreviations:** ADA = anti-drug antibody; EOI=End of Infusion; EOS=End of Study; EOT=End of Treatment; ECOG = Eastern Cooperative Oncology Group; ConMeds = Concomitant medications; CT = computed tomography; MRI = magnetic resonance imaging; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; PD = pharmacodynamics; PK = pharmacokinetics

1. Written consent must be obtained prior to performing any protocol specific procedure.
2. Age, height, gender, ethnicity, and race at screening where possible.
3. Body weight will be measured at screening, predose and postdose at Day 2, D 3, Day 8 and Day 30 visits .. 24-hour liquid input (drinking water) and output (urine) will be recorded post EOI
4. Medical History: includes any significant or relevant diseases, surgeries, or other medical events during the past 5 years and any new conditions arising while enrolled in the study.
5. PE: Full physical examination including the cardiovascular, pulmonary, GI, and nerve system, and skin will be performed at screening and EOS visits, and partial physical examination can be done at other visits to assess any abnormalities or change from baseline, including focused skin and cardiopulmonary examination.
6. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Vital signs will be assessed at screening and on the visits at the clinical research unit. Vital sign will be performed within 30 minutes prior to the infusion, at the EOI (+ 5 minutes) and before every PK sampling. Additionally, blood pressure will be measured every 10 minutes during infusion, every 30 min post EOI up to 6 hours, every 1 hour after 6 hours up to 12 hours post EOI, and every 2 hours until 24 hours post EOI or discharge, and at every outpatient visit. Blood pressure should be measured prior to Colloid osmotic pressure sampling when blood pressure measuring and colloid osmotic pressure sampling are specified to be done at the same time.
7. ECGs (12 lead) will be collected at screening, predose, during infusion(1hr),and EOI, prior to PK sampling during Day 1, and as clinically indicated, and at EOS.
8. Abdominal ultrasound exam will be performed and reviewed during the 28 day screening period, prior to patient check-in on Day -1
9. Only in women of childbearing potential. Urine pregnancy test will be done at screening and EOS, serum pregnancy test will be done pre-dose and on D15, or as clinically indicated.
10. Hematology includes Complete blood count (CBC) (hematocrit (HCT), hemoglobin, red blood cells (RBC), Red Cell Distribution Width (RDW), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), platelets, white blood cells (WBC) with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). Serum Chemistry ALT, AST, ALP, K+, Na+, Cl-, Ca2+, TBIL, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted).
11. HIV screening (Antigen/antibody test), HCV antibodies, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), total hepatitis B core antibody (anti-HBc), IgM antibody to hepatitis B core antigen (IgM anti-HBc), Syphilis.
12. Twenty-four hours urine for D1 after the administration will be collected for 24 hours urine protein. Dipstick is acceptable for other time points. Microscopic analyses if clinically indicated. If  $\geq 2+$  protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio (UPCR) or collect 24h urine.
13. PK samples (Serum albumin) will be collected at pre-dose, 0.5h after dose initiating, EOI, and 0.5h, 4h, 12h, 24h (Day 2), 48h (Day 3), Day 5, Day 8, Day 15, Day 22, and Day 30 post EOI. The exact/actual time to collect blood will be documented.
14. Colloid osmotic pressure will be measured within 30 min predose, every 30 min after dose initiating until EOI, EOI, every 1 hour up to 6 hours post EOI, every 2 hour after 6 hours up to 12 hours post EOI, and every 4 hours until 24 hours post EOI or discharge, 48h (D3), D5, D8, D15, D22, and D30 post EOI. Blood pressure should be measured prior to each colloid osmotic pressure sampling.
15. Blood samples for ADA and Anti-HCP antibody analyses will be collected at pre-dose, D8, D15, D22, and D30 post EOI.

## 2 INTRODUCTION

### 2.1 Background

Human serum albumin (HSA), the main protein of human blood plasma, is a soluble, globular, and unglycosylated monomeric protein. It is responsible for 70-80% of colloid pressure of normal plasma, thus plays a primary role in regulating blood volume by maintaining the colloid osmotic pressure and stabilizing extracellular fluid volume. HSA also functions as a carrier protein for steroids, fatty acids, hormones, and small molecules (1).

Clinically, HSA is widely used for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate, such as adult respiratory distress syndrome, hypovolemia, large-volume paracentesis, ovarian hyperstimulation syndrome, plasma exchange, and ascites caused by cirrhosis of the liver (2, 3). Moreover, HSA is also used as an excipient for vaccines or therapeutic protein drugs and as a cell culture medium supplement in the production of vaccines and pharmaceuticals (4). Many other novel uses for HSA in biological applications have recently been explored, such as carrier of oxygen (5), nanodelivery of drugs (6), and fusion of peptides (7). Currently, clinical used production of HSA is primarily based on collected human plasma, which raises a public health concern with plasma-derived HSA (pHSA) with its potential risk for transmission of blood-derived infectious pathogens, such as bacteria (syphilis, Chagas disease), viruses (including but not limited to HBV, HCV, HIV, HTLV, West Nile virus, CMV) and prions (Mad Cow Disease) (9, 10). The market demand for HSA is estimated around 1000 (Human Serum Albumin Market In-deep Analysis and Experts Review Report 2019-2024) tons per year worldwide. It was reported that the shortage of human plasma led to a rapid increase in price of HSA, which in turn resulted in fake albumin appearing on the market (8). In fact, illegal plasma collection has caused HIV to spread rapidly, creating what are known as AIDS villages in Henan Province in China (11).

The development of screening has been greatly decreased the risk for transmission of blood-derived infectious pathogens, however, the risk has never been eliminated and is always there. To eliminate the potential risk of viral contamination, regulatory agencies in some have encouraged pharmaceutical companies to use non-animal-derived sources for pharmaceutical production (12). Thus, the development of a low-cost method for the production of recombinant HSA (rHSA) is essential as a safer and potentially unlimited alternative to pHSA.

Over the past decades, various expression systems have been used to produce rHSA, including *Escherichia coli* (13), *Saccharomyces cerevisiae* (14), *Kluyveromyces lactis* (15), *Pichia pastoris* (16), transgenic animals (17), and transgenic plants (18–21). Attempts to produce rHSA in tobacco leaves and potato tubers achieved expression levels of 0.02% of total soluble protein (TSP) (18), and expression was increased to 0.2% of TSP by targeting the rHSA to the apoplast of potato tubers (19). Recently, an expression level of 11.1% of TSP was obtained by expressing

rHSA in tobacco leaf chloroplasts (20). More recently, an rHSA expression level of 11.5% of total proteins was achieved in a rice cell culture by a sugar starvation-induced promoter (21). Although rHSA has been successfully expressed in these systems, none of them has proven to be cost-effective at large scale.

Plant seeds, especially cereal crop seeds, are promising vehicles for producing recombinant proteins, because they can achieve high accumulation of recombinant protein, display high levels of protein stability, stored for long periods of time, and are well controlled on a production scale (22, 23). Human lysozyme and lactoferrin produced for oral administration have been successfully expressed in rice seeds (24, 25). Here, Healthgen developed rice seeds as a bioreactor for large-scale production of *Oryza sativa* recombinant HSA (OsrHSA). OsrHSA can be highly and stably expressed in rice seeds and can be processed cost-effectively. OsrHSA was found to be equivalent to pHSA in terms of biochemical properties, physical structure, functions, and immunogenicity.

## 2.2 Risk/Benefit Analysis

Potential risks to subjects receiving OsrHSA are considered to be similar to pHSA, which have been shown to be well-tolerated in general. As there is no difference in *in vivo* efficacy, immunopharmacological activity, safety pharmacology, toxicology, and pharmacokinetic profiles observed between OsrHSA and HpHSA, OsrHSA is expected to have similar clinical effects as HpHSA in indications that are currently approved for HpHSA.

Furthermore, a randomized, double blinded, positive-controlled Phase 1 single dose and dose escalation study to evaluate safety, tolerability, PK and PD (PK/PD) of OsrHSA in adult healthy volunteers (IND Number: CXSL1500135; Protocol Number: HY1001) is ongoing in China. The planned dose levels in this study are 2.5, 5, 10, 15 and 20 g, IV, which are equal to 35.7, 71.4, 142.9, 214.3, and 285.7 mg/kg respectively, assuming a body weight of 70 kg.

The current available data of dose level of 2.5 g (35.7 mg/kg assuming body weight of 70 kg) have been showing an acceptable safety profile. Five subjects have received 2.5 grams, IV, OsrHSA in clinical trial in China. The data indicated that ADA and anti-HCP antibody were negative at 85 days (5 subjects) of post-dosing. No cytokines promotion was found at 28 days (5 subjects) of post-dosing. No allergic and hypersensitivity symptom was observed during or at post-dosing. One subject with SAE of ALT, AST and GGT increasing was observed at 7 day of post-dosing. This subject had a gall-stone with size 1.5\*1.4cm in cystic duct by ultrasound examination. He was diagnosed a biliary obstruction cholecystitis with gall-stone. The subject recovered after 7 days of the symptom and left the investigative center. The safety assessment of SAE was performed by DSMB. The conclusion is that the SAE was caused by biliary obstruction cholecystitis. It is most likely no relevant to OsrHSA. The current data from clinical trial in the China indicated that the risks to subjects receiving OsrHSA is acceptable.

Additional safety and PK/PD data from the Phase 1 study ongoing in China will be provide once available.

## **2.3 In summary, the risk/benefit balance is considered acceptable to administer OsrHSA to healthy volunteers. Preclinical Studies**

### **2.3.1 Non-clinical Pharmacology**

The nonclinical pharmacology program for OsrHSA has been designed to evaluate the *in vivo* efficacy, immunopharmacological activity and safety profiles in animals to predict the pharmacologic profile of OsrHSA in human. The *in vivo* efficacy of OsrHSA was evaluated in the treatment of ascites of high-fat diet induced hepatic cirrhosis in a Wistar rat model, as well as in hemorrhagic shock model using male Japanese rabbits. Similar efficacy of OsrHSA and HpHSA has been demonstrated in these two animal disease models.

The effects of OsrHSA on the immune function of mammalian systems were investigated in three studies. No active systemic anaphylaxis (ASA) reaction was induced in rabbits, after primed with OsrHSA/CFA and challenged with OsrHSA/IFA, with no elevated total IgG, IgM, IgA, IgE production detected. No passive cutaneous anaphylaxis (PCA) induced in the guinea pigs after transfer the sensitized serum from the rabbits. 1/1436 and 0/200 anti-HCP IgE antibody was detected in a preliminary non GLP study and an US-GLP study, suggesting a low risk of the HCP from *Oryza sativa* in inducing allergic responses in humans. T-cell mediated DTH study confirmed that OsrHSA and HpHSA were weakly immunogenic in soluble forms as a foreign antigen to mice. If administered as soluble proteins, OsrHSA was unable to induce DTH response in mice, which suggested a low risk of inducing type IV hypersensitivity in human subjects.

### **2.3.2 Non-clinical Pharmacokinetics**

The pharmacokinetic (PK) and toxicokinetics (TK) profiles of OsrHSA were characterized in rats and monkeys following intravenous administration, which is the intended route of administration in human. In order to distinguish exogenous OsrHSA from endogenous rat serum albumin, OsrHSA was labeled with <sup>125</sup>I by Chloramine-T method before administration.

Distribution, metabolism and excretion was evaluated in the single-dose PK study in rats. OsrHSA is expected to behave like HSA, an endogenous protein, in drug transportation as well as in interactions with CYP enzymes or other drug transporters. Therefore, no pharmacokinetic drug interaction studies of OsrHSA were conducted.

HpHSA was included as a benchmark control and compared with OsrHSA side-by-side in several pharmacokinetic and toxicokinetics studies. HpHSA and OsrHSA showed similar PK and TK profile among all the studies, except HpHSA showed stronger immunogenicity in rats following repeat dose administration.



### 2.3.3 Safety Pharmacology and Toxicology

Safety pharmacology was conducted in mice to evaluate the effect on CNS function, as well as in cynomolgus monkeys to evaluate the effect on cardiovascular and respiratory functions. HpHSA was included as a control in all these studies to detect off-target or impurity induced side effects.

Because of pre-clinical and clinical experiences over many years of using with HpHSA, the full battery of toxicology studies conducted were not to evaluate the pharmacological and toxicological effects of the active ingredient albumin in OsrHSA, but mainly to evaluate unexpected toxic activities due to the impurities in the OsrHSA drug product. Evaluation of the potential risk to humans receiving OsrHSA was conducted in a series of US-GLP compliant toxicology studies according to 21 CFR 58.

While albumin are variable among the species, the tertiary structures and biological functions are highly conserved (Nurdiansyah, R., Rifa'I, M. 2016). Since the MOA of albumin for treatment of circulatory dysfunction is attribute to the increase of plasma volume, which is similar among species, therefore, multiple species (both rodent and non-rodent) were included in the toxicology evaluation.

Single-dose study in rats, 2-week repeat-dose with 4-week recovery phase studies in rats and monkeys were conducted to assess the toxicity and toxic organs as well as the reversibility, persistence, or delayed occurrence of any safety findings. Among these studies, the toxic levels and toxic organs identified were similar in animals treated OsrHSA and HpHSA. The treatment-related clinical and pathological changes were directly resulted from the biologic functions of albumin, and the daily injection induced fluid overload and increased blood pressure. No OsrHSA specific toxicity was identified, indicating the entire formulation of OsrHSA, including all possible impurities, exerted similar biological function, as well as toxicity at high dose, as that of the formulation of HpHSA. Both OsrHSA and HpHSA were immunogenic in animals via *i.v.* dosing. Formation of ADA was prevalent in rats and monkeys, although no impact on TK or systemic exposures were observed. Regardless with HSA formulation administered, ADA formed can be cross-recognized by the other HSA reagent, indicating that these ADA were against the same epitopes common in both OsrHSA and HpHSA, further supported the tertiary structure similarity between OsrHSA and HpHSA.

A full battery of study was conducted to evaluate the genotoxicity of OsrHSA as required in ICH S2 (R1) on Genotoxicity testing and Data Interpretation for Pharmaceuticals Intended for Human Use, June 2012. Ames test, chromosomal aberration test as well as *in vivo* micronucleus study confirmed that OsrHSA has no potential genotoxicity.

Host cell protein (HCP) is the main impurity in the formulations of OsrHSA. The potential toxicity and immunogenicity induced by HCP was evaluated in a 2-week daily repeat *i.v.* dose non-GLP study in SD rats. No clinical findings were observed for 25 µg/kg HCP, that is equivalent to the possible HCP presented in 5 g/kg OsrHSA.

### 3 OBJECTIVES AND ENDPOINTS

#### 3.1 Objectives

##### Primary Objectives:

- To assess the safety and tolerability profile of OsrHSA when IV administered as single dose

##### Secondary Objectives:

- To characterize the PK of OsrHSA when IV administered as single dose
- Immunogenicity profiles of OsrHSA when IV administered as single dose

##### Exploratory Objectives:

- To assess changes in serum albumin level, colloid osmotic pressure, blood pressure and body weight when IV administered as single dose

#### 3.2 Endpoints

##### Primary Endpoints

- 1) Safety and tolerability profile including adverse events, changes in safety assessment parameters (e.g. vitals, ECGs, clinical laboratory results)

##### Secondary Endpoints

- 1) PK parameters:  $AUC_{0-\infty}$  and  $AUC_{0-t}$ ,  $C_{max}$ ,  $t_{1/2}$ ,  $CL$ ,  $V_{ss}$ , etc.
- 2) ADA: Samples confirmed to be positive for ADA will be further tested for NAb.

##### Exploratory Endpoints

- Changes in serum albumin level and colloid osmotic pressure
- Changes in body weight and blood pressure

## 4 STUDY DESIGN

### 4.1 Overall Study Design

This is a Phase 1 randomized, double blinded, placebo-controlled, single dose escalation study in healthy volunteers to evaluate safety, tolerability, PK, PD and immunogenicity of OsrHSA (See [study design schema](#)).

### 4.2 Study Process

The trial will include a screening period, treatment period, and follow-up period of 30 days after administration. The screening period will be up to 28 days prior to investigational product administration. The screening process will initiate upon completion of the informed consent process. Once consent is provided by each participant, a thorough screening process will take place, including detailed medical history, physical examination, vital signs, concomitant medications, safety labs (see Table 1), 12 lead electrocardiogram, urine pregnancy test, urinalysis, serology panel (refer Table 1), assessment of inclusion and exclusion criteria. Upon completion of the screening, qualified subjects will be randomized to OsrHSA or placebo (6:2). Each enrolled subject will receive one single assigned dose of OsrHSA or placebo. The investigator and subjects will be blinded to treatment assignment. During the study, subjects will be evaluated for safety and toxicity, PK/PD, and activity of OsrHSA.

OsrHSA or placebo will be administered as single IV infusion at a rate lower than 2 ml/ min to the subjects. The actual start and stop times of the infusions, along with any interruptions in the infusion will be recorded. Subjects will have end-of-study (EOS) follow-up visits on Day 30 after infusion.

The planned doses are 20, 40, 80, 140, and 200 mg/kg (Table 2), dose level(s) higher than 200 mg/kg might be an option(s) based on emerging data from this study and ongoing China clinical trial, if that is the case, an amendment will be submitted.

The protocol for the repeat dose study will be submitted as an amendment to the IND after the single dose study has been completed and analyzed. The dose schedule of the repeat dose study will be based on results obtained from the single dose study. The safety of the dose that will be used in the repeat dose study will be established before the initiation of the repeat dose study.

Dose escalation will occur sequentially after review of safety data for each dosing cohort by the safety review committee (SRC). Dose escalation to the next dose level will proceed uninterrupted as long as no pre-defined DLT or stopping criteria are met.

#### 4.2.1 Definition of Dose Limiting Toxicity (DLT):

AEs will be graded according to the FDA Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. DLT is

defined according to the criteria below as any TEAEs occurring during the DLT observation period (7 days) and considered to be related to OsrHSA:

*Any Grade  $\geq$  3 AE or laboratory abnormality as defined in the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*

All Grade 3 toxicities for vital signs and laboratory parameters must be confirmed with a repeat measurement obtained within 1 hour or as soon as possible for vital signs and within 24 hours for laboratory parameters.

**Table 2 Dose Escalation Schedule**

<b>Dose Escalation Level</b>	<b>Dose (mg/kg)</b>	<b>Subjects (OsrHSA:placebo)</b>
cohort 1	20, IV	8(6:2)
cohort 2	40, IV	8(6:2)
cohort 3	80, IV	8(6:2)
cohort 4	140, IV	8(6:2)
cohort 5	200, IV	8(6:2)

#### **4.2.2 Dose-escalation Criteria:**

Tolerability and safety of subjects in a cohort will be reviewed by the SRC which is comprised of an independent Medical Monitor, site Principal Investigator, and Sponsor Study Director. Dose escalation may be stopped at any time based upon the Sponsor or Investigator's clinical assessment or judgment. Upon completion of the DLT observational period (first week after dosing), the SRC will examine safety data through Week 1 for each dose cohort in combination with all available, previously accumulated safety data, as well as available PK data, if any, from all subjects enrolled in the study to date. All cohorts will enroll 8 subjects (safety data from at least 6 or 7 subjects would be needed for SRC meeting, in case a subject discontinues the study), if no more than 2 out of 8 subjects experiences DLT as defined in the section 4.2.1, dose will be escalated to the next dose level.

#### **4.2.3 Subject Stopping Criteria:**

Dosing will be permanently stopped for any individual subject experiencing any of the following:

- Any SAE, regardless of causality to the study drug.

- Subject experience DLT.
- Hypersensitivity or anaphylactic reaction following start of infusion.
- Medical condition that is judged by the Investigator as to jeopardize the subject's safety if he or she continues to receive the study drug.
- QTc prolongation defined as QTcF increasing  $\geq 60$  msec and persisting for at least 10 minutes or QTcF  $> 500$  msec and persisting for at least 30 minutes, or episode of torsade de pointes.

#### 4.2.4 Dose Escalation Stopping Criteria:

Dose escalation will not occur if any of the following criteria are met:

- Subject stopping rules met for  $\geq 2$  subjects in the same cohort suggesting to the Investigator that other subjects in the cohort are at risk for similar adverse drug reactions.
- Any SAE as defined in the section 10.1 in any participant receiving study drug unless obviously not related.
- $\geq 2$  out of 8 subjects experience toxicity  $\geq$  Grade 3 as defined in the Food and Drug Administration (FDA) Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*.

The safety review will initially be performed on blinded data, and if any of the above criteria are met, the cohort will be subsequently unblinded to all SRC members and the safety and tolerability reassessed. Upon unblinding, the dose may be determined to be safe and tolerable, on the basis of events observed in the OsrHSA vs. placebo groups, allowing for dose escalation to proceed.

#### 4.3 Rationale for Starting Dose and Maximum Dose Selection

As there is no difference in *in vivo* efficacy, immunopharmacological activity, safety pharmacology, toxicology, and pharmacokinetic profiles observed between OsrHSA and HpHSA, OsrHSA is expected to have similar exposure and clinical effects as HpHSA in indications that are currently approved for HpHSA. The starting dose and the maximum dose for proposed US clinical trial of OsrHSA were selected based on the current clinical doses of HpHSA, which are in the range of 5 to 100 g (0.071 – 1.429 g/kg) [ Guidelines for Intravenous Albumin Administration at Stanford Health Care. Stanford Health Care. Created: 03/2017 Pharmacy Department] depending on the condition for which HpHSA is used to treat, for example, 50 to 100 g, IV, over 4 hours, repeat at 4 to 12 hours intervals as needed, can be used to treat ovarian hyperstimulation syndrome.

*Regarding the potential toxicity of host cell proteins, daily i.v. infusions of 25 µg/kg HCP induced no clinical findings in rats. Thus, the proposed 1.5 g (0.021 g/kg, contains 0.10 µg/kg possible HCP) starting dose provides 40-fold safety margin from the 25 µg/kg HCP rat dose (4 µg/kg HED, converted based on BSA).*

In an ongoing randomized, double blinded, positive-controlled Phase 1 single dose and dose escalation study of OsrHSA in adult healthy volunteers for safety, tolerability, PK and PD (PK/PD) study in China, five healthy volunteer were administered single dose of 2.5 g OsrHSA (35.7 mg/kg assuming body weight of 70 kg), IV. The data indicated that ADA, anti-HCP antibody are negative at 85 days (5 subjects) of post-dosing. No cytokines promotion was found at 28 days (5 subjects) of post-dosing. No allergic and hypersensitivity symptom was observed during dosing or post dosing. One subject experienced abdominal pain and a transient 20 x elevation in ALT/AST. The subject was recovered and the AEs were considered highly likely due to pre-existing cholelithiasis and cholecystitis by DSMB. Another subject was found a transient 2.4x ALT/AST elevation without any symptoms and signs. Please see M2.7 for the detailed clinical data.

The next dose levels of 5.0, 10, 15, and 20 g OsrHSA are being tested in healthy volunteer in China, data will be updated when data available.

In summary, OsrHSA has shown acceptable safety profile at dose level of 35.7 mg/kg. The proposed starting dose of 20 mg/kg in the current protocol is justified by 1.8-fold lower than the tested dose in China and considered to be safe.

## **5 PATIENT POPULATION**

### **5.1 Number of Subjects and Description of Population**

This study will enroll up to 40 healthy male or female subjects, 8 subjects for each of 5 cohorts, 18-55 years old, or more subjects might be recruited based on emerging data from this study and ongoing China clinical trial. Subject Selection and Numbering:

### **5.2 Inclusion Criteria**

Subjects must meet all the following criteria to be enrolled in the trial:

1. Able to understand and willing to sign the ICF
2. Healthy male and female subjects, non-smokers, 18-55 years of age, non-smokers, or subjects must have been non-smoking for at least 3 months prior to their screening visit
3. Has adequate venous access
4. With no significant medical history, and in good health as determined by detailed medical history (neurological, endocrinal, cardiovascular, pulmonary, hematological, immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease), full physical examination,

vital signs, 12-lead electrocardiogram (ECG), urinalysis and laboratory tests at screening. For eligibility purposes, abnormal laboratory or vital signs results may be repeated once if abnormal result is observed at the initial reading. Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements.

5. Subjects must have adequate organ function according to the following laboratory values:
  - Bone marrow function (absolute neutrophil count  $\geq 1500/\text{mm}^3$  and platelet count  $\geq 100,000/\text{mm}^3$ )
  - Adequate liver function [alanine aminotransferase (ALT)  $\leq 1.5 \times$  upper limit normal (ULN) and alkaline phosphatase  $\leq 1.5 \times$  ULN, total bilirubin  $\leq 1.5$  mg/dL]
  - Adequate renal function creatinine clearance  $\geq 60$  mL/min based on Cockcroft- Gault equation, or serum creatinine level  $\leq 1.5$  times the ULN.
6. Be a female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal and have an FSH  $> 40\text{mIU/mL}$ , or surgically sterile [defined as having a bilateral oophorectomy, hysterectomy or tubal ligation]) or agree to one of the following to prevent pregnancy and, if a woman of childbearing potential, have a negative urine pregnancy test at screening:
  - Practicing abstinence
  - If a sexually active woman of childbearing potential (sexually active with a non-sterile male partner) agrees to prevent pregnancy by using double methods of contraception as follow until at least 30 days after the administration of the investigational product:
    - a. simultaneous use of intra-uterine contraceptive device, placed at least 4 weeks prior to study drug administration, and condom for the male partner;
    - b. simultaneous use of hormonal contraceptives, starting at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner;
    - c. simultaneous use of diaphragm with intravaginally applied spermicide and male condom for the male partner, starting at least 21 days prior to study drug administration.
  - Male subjects who are not vasectomized for at least 6 months and who are sexually active with a non-sterile female partner must agree to use double methods of contraception below

from the first dose of randomized study drug until 90 days after their dose and must not donate sperm during their study participation period:

- a) simultaneous use of a male condom and, for the female partner, hormonal contraceptives (used since at least 4 weeks) or intra-uterine contraceptive device (placed since at least 4 weeks);
  - b) simultaneous use of a male condom and, for the female partner, a diaphragm with intravaginally applied spermicide.
7. Body mass index (BMI) 18-30 kg/m<sup>2</sup> and body weight  $\geq$  50.0 kg for males and  $\geq$  45.0 kg for females.
  8. Blood pressure  $\leq$  139/89 mm Hg.
  9. Subjects are able to follow the study protocol and complete the trial.
  10. At least 25% of the enrolled subjects will be of Asian descent, defined as Chinese, Japanese, Korean, Vietnamese, Hmong, and their offspring.

### 5.3 Exclusion Criteria

Subjects who meet any of the following criteria cannot be enrolled:

1. History of severe infection within 4 weeks to dosing.
2. Signs and symptoms of any active infection regardless of severity within 2 weeks prior to dosing.
3. Meals & Dietary Restrictions: No seafood or high-fat food will be served during confinement in the clinical center
4. Subjects who have any history of allergy to food or drug will be excluded ( Including allergies, hypersensitivity, or intolerance to rice or rice products )
5. Use of any prescription drugs, herbal supplements, or nonprescription drugs including oral anti-histamines (for seasonal allergies) within 1 month or 5 half-lives (whichever is longer) prior to study drug administration, or dietary supplements within 1 week prior to study drug administration, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study. Over-the-counter multivitamins will be permitted. If needed, paracetamol/acetaminophen may be used, but must be documented in the Concomitant medications/Significant non-drug therapies page of the source data. Any questions of concomitant medications should be directed to the Sponsor.
6. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the first dosing, administration of a biological product in the context of a clinical research study within 90 days prior to the first



dosing, or concomitant participation in an investigational study involving no drug or device administration.

7. Donation of blood 12 week prior to dosing.
8. Pregnant, or nursing females.
9. A history of substance abuse, psychiatric and psychological condition that, in the judgment of the investigator, may interfere with the planned treatment and follow-up, affect subject compliance or place the subject at high risk from treatment-related complications
10. A history of severe allergic reaction to any HpHSA component.
11. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTcF interval >450 milliseconds [ms])
12. History of or active obstructive disease in biliary tract, liver, kidney and spleen defined by ultrasound
13. Subjects who test positive for hepatitis B or C. (no matter carriers or active will be excluded from the study)
14. Subjects who test positive for Syphilis, Human immunodeficiency virus (HIV) positive will also be excluded from the study
15. Immunization with a live or attenuated vaccine is prohibited within 4 weeks prior to study drug administration. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed)
16. Positive Ig E and Ig G against rice at screening
17. History of significant alcohol abuse within one year prior to screening or regular use of alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]) or positive alcohol breath test at screening
18. History of significant drug abuse within one year prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year prior to screening
19. Positive urine drug screen, cotinine test, or alcohol breath test at screening
20. Any reason which, in the opinion of the Qualified Investigator, would prevent the subject from participating in the study.

#### **5.4 Meals and Dietary Restrictions**

Subjects will receive a standard diet whilst resident in the clinical center. For standardization purpose, the study drug infusion will start at least 30 minutes after subjects have been served a

light breakfast. No food will be allowed until at least 1 hour after the end of infusion. Standardized meals will be served at appropriate times thereafter.

Water will be provided *ad libitum* at all times.

In addition, subjects will be required to abstain from:

- food containing poppy seeds within 24 hours prior to admission;
- food or beverages containing xanthine derivatives or xanthine-related compounds (coffee, black/green tea, chocolate) or energy drinks from 48 hours prior dosing until EOS;
- dietary supplements within 1 week prior to study drug administration until EOS, unless, in the opinion of the Investigator and Sponsor, the dietary supplement will not interfere with the study;

### **5.5 Tobacco, Alcohol and Illicit Drugs**

Refrain from intake of alcoholic beverages from 72 hours prior to study treatment administration until Day 8 postdose. After Day 8, subjects are discouraged from consuming alcohol until the completion of the study, but may consume no more than 1 unit of alcohol per day.

Subjects will be required to abstain from using nicotine products, or soft or hard drugs from screening and throughout the study.

### **5.6 Medication**

Use of any prescription, herbal supplements, or nonprescription drugs will be prohibited within 1 month or 5 half-lives (whichever is longer) prior to study drug administration and until EOS, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study. No concomitant drug therapy will be allowed during the study except one(s) required for the medical management of an adverse event.

Any concomitant medication use other than the occasional use of acetaminophen will be evaluated on a case-by-case basis by the Principal Investigator or a physician. The use of hormonal contraceptives will be allowed and documented. All concomitant medication use will be documented.

### **5.7 Activity**

Subjects should refrain from strenuous exercise for 48 hours before admission to the clinical center and throughout the study. Subjects may participate in light recreational activities during the study (eg, watching television, reading).

Subjects will be advised not to donate blood or plasma from at least 12 weeks before study drug administration and for at least 3 months after the last dose administration.

For safety reasons, subjects will be required to remain semi-reclined and avoid lying down or sleeping for the first 4 hours after the end of study drug infusion. However, failure of subjects to comply with these requirements does not constitute a deviation from the protocol if it is medically necessary, procedurally required, or to go to the bathroom. When appropriate, subjects will be accompanied by a staff member during ambulation.

## **5.8 Randomization and blinding**

Subjects in the clinical site will be 6:2 randomized to receive either the study product or placebo prior to dosing, the randomization code will not be available to the Bioanalytical Division until the clinical and analytical phases have been completed for each cohort.

Both the principal investigator and subjects will be blinded as to whether a subject is receiving study product, or placebo. A designated person in the Investigational Pharmacy will dispense the appropriate drug accordingly. The Safety Review Committee can request unblinded randomization scheme in order to evaluate the data.

Each bottle administered to subjects will have a unique code, and quick unblinding will be performed by Investigational Drug Pharmacy, the principal investigator, or the sponsor, should a medical emergency arise for a participant.

Upon completion of the study participation, all subjects will be unblinded

## **6 STUDY INTERVENTION**

### **6.1 Study Drug Description**

OsrHSA drug product is presented as a slightly viscous, yellow to brownish clear liquid packed in Type I neutral borosilicate moulded glass vial capped with chlorobutyl rubber stopper with Polytetrafluoroethylene (PTFE)/Polyhexafluoroethylene film and plastic-aluminum seal. Each vial contains 10 g OsrHSA protein, 0.261 g sodium octanoate, 0.409 g sodium chloride, pH6.4~7.4. The total volume is 50 ml.

Normal Saline (0.9% Sodium Chloride) will be used as the placebo.

### **6.2 Study Drug Packaging and Labeling**

OsrHSA drug product is packed in Type I neutral borosilicate moulded glass vial capped with chlorobutyl rubber stopper with Polytetrafluoroethylene (PTFE)/Polyhexafluoroethylene film and plastic-aluminum seal. There will be a carton package. The labels for carton and vial are shown below.

Recombinant human serum albumin from *Oryza sativa* (OsrHSA). 20% solution with 10g of drug.

#### **6.2.1 Drug Storage and Handling**

OsrHSA drug product is stored at 2-8°C, protected from light. At time of use, the drug product vial is directly connected to the infusion line equipped with a 0.2µm in-line filter and administered via IV infusion.

#### **6.2.2 Study Drug Compliance and Accountability**

The site should record and maintain shipping and receiving records of the study drug, and report to the Sponsor immediately any defect or issues with quality, quantity or interruption in cold-chain shipping.

The site will maintain accurate dosage preparation records and should ensure that all pertinent/required information on the preparation and administration of the dose is captured in source documents, and appropriate dosing information is entered onto eCRFs. Such information should be made available to the Sponsor's site monitoring representative(s) during monitoring visits.

#### **6.2.3 Disposal and Destruction**

Upon termination of the study, or at the request of the sponsor, the pharmacist (or designee) must return the study drugs to Sponsor, unless it is destroyed at the clinical site as agreed upon by both the sponsor and the clinical site.

#### **6.2.4 Treatment Allocation and Administration, Dosing Regimen**

This is a Phase 1 randomized, double blinded, placebo-controlled study. Subjects will be randomized. Both subjects and investigator will be blinded.

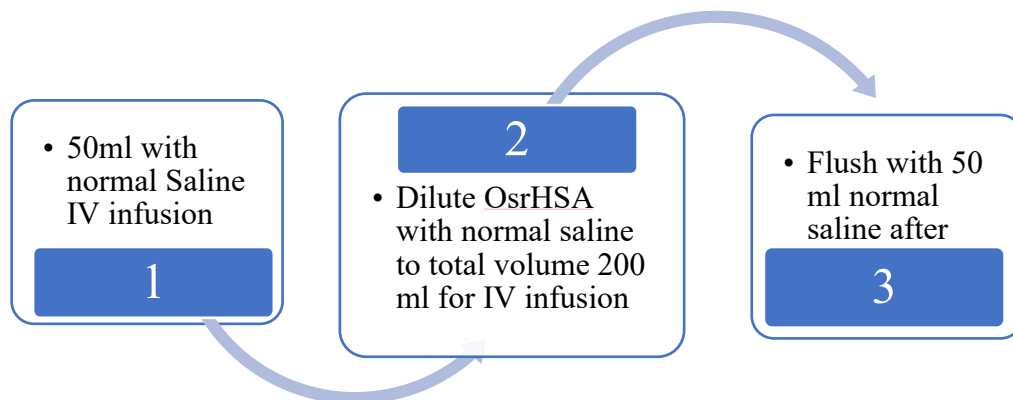
1. Parenteral drug products should be prepared by using appropriate aseptic technique, and inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2. Treatment Allocation and Administration: OsrHSA will be diluted with normal saline to a total volume of 200ml.

The total infusion time will be 2hr ± 20min.

The OsrHSA infusion rate is lower than 2ml/min. The procedures used for administration are following:

- First, set up intravenous channel and intravenous injection of 50 ml saline. The infusion rate for normal saline will be 5ml/min.
- Second, OsrHSA or placebo will be administered via an infusion line equipped with a 0.2µm in-line filter. And monitor for infusion-related AEs during administration. The rate of intravenous should be lower than 2 ml/ min and cautions should be taken. Dose interruption based on intolerability will be captured in the monitoring of infusion start and stop times.
- Third, flush with 50ml normal Saline after the dose. The infusion rate for normal saline will be 5ml/min.



All dose administrations will be performed in the clinical center under the supervision of appropriately trained staff.

Further detailed instructions on handling and administration of study drug is described in the separate Pharmacy Manual.

### 6.3 Duration of Treatment

This is a single dose study.

## **6.4 Removal from Study Treatment and off-Study Criteria**

Participation in this research study is completely voluntary. Subjects are free to withdraw from this study at any time by informing the investigator. If a subject, for whatever reason, no longer appropriate to continue receiving study therapy, they will be notified and withdrawn from the study. Furthermore, if the subject is non-compliant (e.g. non-compliant with visits, concomitant medications.) they will be withdrawn from the study and a replacement subject may be recruited.

Additionally, prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

### **6.4.1 Criteria for Removal from Study Treatment**

- Completion of protocol therapy
- Participant requests to be withdrawn from the study
- Investigator discretion
- Lost to follow-up or noncompliance
- AEs or safety concerns by Investigator or Sponsor
- Positive alcohol test, cotinine test, or drug screen
- Positive pregnancy test.

### **6.4.2 Off-Study Criteria**

Once a subject is taken off study, no further data can be collected.

- Participant request to be withdrawn from study
- Subject withdrawal from the follow-up period
- Subject completed all protocol required follow-ups
- Death
- Screen failure

### **6.4.3 Subject Replacement**

Subjects who do not receive the full dose of study drug, or who withdraw from the study or with significant protocol violations may be replaced at the discretion of the investigator after informing the Sponsor.

## 7 STUDY ASSESSMENT AND EVALUATIONS

### 7.1 Description of Assessment Procedures

Below are additional descriptions of study assessments not detailed in [Table 1](#).

**Recording of AEs:** AEs should be documented and recorded per Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. After signing ICF and before the administration, only SAEs related to study intervention will be recorded. All AEs will be recorded once dosing starts and subjects must be followed for AEs for 30 days after the administration, or until all drug related toxicities have resolved, whichever is later. After 30 days only SAEs considered related to study treatment will continue to be recorded.

### 7.2 Blood Samples for PK evaluations

Blood samples will be collected at pre-dose, 0.5h after dose initiating, EOI, and 0.5h, 4h, 12h, 24h (Day 2), 48h (Day 3), Day 5, Day 8, Day 15, Day 22, and Day 30 post EOI, from all subjects to determine the serum concentration of OsrHSA using a validated immunoassay for PK analyses. Approximately 3 mL blood will be collected at each of the following time points. Serum will be separated and stored for bioanalysis of OsrHSA concentration with a validated assay. The exact/actual time to collect blood will be documented.

An additional blood sample should be collected from subjects experiencing unexpected and/or serious AEs if possible.

The sampling schedules are seen in [Table 1](#).

### 7.3 Immunogenicity Evaluations

Blood samples for ADA analyses will be collected at pre-dose, D8, D15, D22, and D30 post EOI

## **8 DATA COLLECTION AND MANAGEMENT**

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Hardcopies of the study visit worksheets will be used as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into 21 CFR Part 11-compliant data capture system provided. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Only individuals who have received training on the EDC are allowed to make eCRF entries, corrections, and alterations. Training must be documented and a log of all EDC users and their rights within the system be maintained. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct.

Any outstanding entries must be completed immediately upon notice. No blank sections should be left on CRF and explanations has to be recorded for all missing data. All source documents should be retained. All essential documents should only contain subject coded identifiers and no personal identifying information should be transmitted.

### **8.1 Study Record Retentions**

After completion of the study and when all collected data are validated, the database will be locked, pursuant to the prior approval by the Sponsor (or its designee). Final data will be extracted from the EDC system and delivered in the form of SAS<sup>®</sup> datasets. A Portable Document Format (PDF) copy of the eCRF will be produced for each study subject and included in the final delivery.

All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with sponsors/CROs security standards. Each Subject will have identifiers that will be kept at the study sites.

If clinical site/sponsor becomes aware of loss or destruction of data due to a major breach occurrence that has jeopardized subject confidentiality and trial data, the IRB will be notified.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing



applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## **8.2 Protocol Deviations**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the Sponsor if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

It is the responsibility of the site investigator to use continuous vigilance to identify and report, when applicable, deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and if applicable, in eCRFs and study reports, in coordination with the sponsor or their designated CRO. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the requirements of the reviewing IRB.

## **8.3 Publication and Data Sharing**

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee.

## **9 REGULATORY HUMAN SUBJECT PROTECTION AND REGULATORY OVERSIGHT**

### **9.1 Informed Consent Processes and Documentation**

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written ICFs and any other written information to be provided to the participants. Participants will be asked to read and review IRB-approved ICFs and other written information. ICF should include detailed description of study procedures, risk and benefits, directions, participant's rights, compensation if applicable, and contact of Human Subject Protection Services. Additionally, investigator will explain the research study to the participant in terms suited to the participant's comprehension and answer any questions that may arise. Investigator should explain their rights as research participants, study procedures, risk and benefits, anticipated adverse effects. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. ICF should be signed prior to any interventions for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participant will be given a copy of the signed consent form and the original consent form will be kept as a permanent record.

### **9.2 Confidentiality and Privacy**

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

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product 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 study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management group at the designated CRO. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by CRO staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at the CRO or Sponsor until further data integration with future studies of OsrHSA.

### **9.3 Conflict of Interest**

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.

## 10 SAFETY REPORTING

### 10.1 Definition of Adverse Event

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial whether or not the event is considered related to the treatment or clinically significant.

For this clinical trial, AEs will include any events reported by the subject, any new medical conditions, and symptoms, any new abnormal findings on physical examination or laboratory evaluation. Additionally, any worsening of a pre-existing condition or abnormality will also be considered as an AE.

All AEs must be recorded on eCRF. All AEs must be followed return to baseline or stabilizes.

#### Serious adverse events (SAE)

A serious adverse event is defined as any adverse experience that meets any of the following criteria:

- Results in death;
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization. Additionally, complications occurring during hospitalization are also considered AEs.
- Results in persistent or significant disability or incapacity (This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.);

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

The following hospitalizations are not considered to be SAEs because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug

- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

## Adverse Reaction

Any AE caused by a drug is considered an adverse reaction.

### 10.2 Causality of AEs

Causality assessment has become a common routine procedure in pharmacovigilance. Causality assessments can decrease disagreement between assessors, classify relationship likelihood and improvement of scientific evaluation.

Limitations of causality assessment are following:

It can NOT assess accurate quantitative measurement of relationship likelihood

It can NOT distinguish valid from invalid cases

It can NOT prove the connection between drug and event

It can NOT quantify the contribution of a drug to the development of an adverse event

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the 2 categories below. In a clinical trial, the study product must always be suspect.

**Related:** The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

**Not Related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

### 10.3 Categorization of AEs

AEs will be graded according to the FDA Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* and reported in the detail indicated on the CRF. The definitions are as follows:

Grade 1 Mild: discomfort noticed, but no disruption to daily activity

Grade 2 Moderate: discomfort sufficient to reduce or affect normal daily activity

Grade 3 Severe: Inability to work or perform normal daily activity

## Grade 4 Potentially Life-threatening

### **10.4 Reporting of SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs)**

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported by investigator to the sponsor **within 24 hours** (and IRB as required) of first becoming aware of the SAE. The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting

SAEs will be collected by the investigator from day 1 through 30 days after the administration of study medication. SAEs that occur within 30 days following cessation of the study treatment, must also be reported within the same timeframe. Any SAE that is judged by the investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor (or its designee) within 24 hours of receipt by the investigator. All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible. To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, reports of radiographic studies, and clinical laboratory reports should be obtained.

In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report, if performed. These records should be reviewed in detail, and the investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the investigator should consider whether the event is related or not related to study drug.

### **10.5 IRB Reporting**

The investigators will report to the IRB the following according to the requirements of reviewing IRB:

- All SAEs, except deaths due to progressive disease
- Non-compliance to GCP or protocol deviations as required by IRB

IND Safety Reports and any unexpected incidences or problems during the trial may be also reportable to the IRB as per IRB requirement.

## **10.6 Quality Assurance and Quality Control**

Quality control (QC) procedures will be implemented to assure that any missing data will be communicated with sites for clarification and resolution.

Standard Operating Procedures (SOPs) should be available to monitors. Monitors will verify that all the clinical trial procedures are conducted, documented and reported in compliance with the protocol, ICH, GCP, GLP, GMP and other applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## **10.7 Study Monitoring Plan**

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the Sponsor.

Details of clinical site monitoring will be documented in a separate Study Monitoring Plan (SMP). The SMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. In general monitoring visits would include pre-study visits (to qualify the site and investigators), study initiation visit, interim visits at appropriate frequency based on recruitment speed and need to clean data for dose-escalation decisions, and study closeout visits after database lock.

Independent audits may be conducted by the sponsor to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the SMP.

Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

A monitor(s)/sponsor representative(s) will meet with the investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording study data. After enrollment of the first subject, a monitor(s)/sponsor representative(s) will be assigned to periodically monitor each investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) and/or ICH guidelines were followed.

The investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed CRFs, signed consent forms and other study related documents are readily available for review.

FDA regulations require the Investigators to facilitate monitoring process. Monitors will evaluate adherence to the protocol, regulations, SOPs, human subject protection, study data, specifically data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring

### **10.8 Study Closure**

The investigator may terminate the study at any time in the interest of subject welfare. The sponsor may terminate the study prematurely at any time. Reasons for the closure of an investigational site or termination of a study may include:

- The Investigator fails to comply with the protocol or ICH/GCP guidelines
- Safety concerns
- Inadequate recruitment of subjects by the investigator
- Completion of the study

If the clinical study is prematurely terminated or suspended, the sponsor or CRO representative will inform the investigator and the regulatory authorities of the termination/ suspension and the reasons for the termination/suspension as appropriate. The investigator should promptly notify the IEC/IRB of the termination or suspension and provide reasons. The sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause.

Premature termination of the study by either PI or sponsor will be governed under the terms of the contract between both parties.

### **10.9 Safety Review Committee (SRC)**

To ensure the safety of study subjects and integrity of the study data, a Safety Review Committee (SRC) consisting of the study Investigators, Study Director, designated Medical Monitor and/or other key study personnel will convene to review cumulative data for the study. SRC will conduct dose decision teleconference meeting before each dose escalation.

Before each dose escalation, the Investigators, Study Director and Medical Monitor(s), together, will review the safety data from the current cohort after enough subjects (7-8) have completed the first week. It will be determined whether escalation to the next dose level can proceed or whether dose level should be de-escalated.





## **11 STATISTICAL CONSIDERATIONS**

### **11.1 General Statistical Considerations**

Descriptive statistics will be utilized for all safety, efficacy, and PK parameters. Data will be summarized using descriptive statistics (number of subjects, mean, and median, standard deviation, minimum and maximum) for continuous variables and using frequencies and percentages for discrete variables.

In addition to descriptive summary, statistical testing will be performed to provide inferential summaries of group/subgroup comparison of endpoints. Univariate analyses will be conducted to determine the effects of key patient and disease characteristics on study endpoints, e.g., Two-sample *t*-test or Wilcoxon rank sum test will be used for continuous variables as appropriate and Chi-square test or Fisher's exact test for categorical variables. Kaplan-Meier method or log-rank test will be provided for time-to-event endpoints. For comparison of more than 2 groups, ANOVA test or Kruskal-Wallis test will be carried out. Multivariate analyses may be conducted to examining relationship between multiple variables and endpoints.

### **11.2 Determination of Sample Size**

An estimated total of 40 subjects will enroll in this study. The sample size for this study was determined based on clinical, rather than statistical considerations. A projected sample size of 8 subjects per dosing cohort is considered to be of reasonable size to achieve the objectives of this single dose escalation trial. Other factors may contribute to the final sample size, which is dependent upon the observed safety and tolerability profile, and determines the number of subjects per dose cohort, number of replacements, as well as the number of dose escalations required to achieve the maximal proposed dose of the study drug.

### **11.3 Population Analysis**

#### **11.3.1 PK and PD Population**

The PK population will include all subjects who have at least one post-dose blood sample providing evaluable PK data.

#### **11.3.2 Safety Population**

The safety population will include all subjects who receive the investigational drug. The safety analyses population will be the primary population for evaluating treatment administration, compliance and safety in the study.

## 11.4 Statistical Analysis

### 11.4.1 PK Analysis

PK parameters will include  $T_{max}$ ,  $C_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $t_{1/2}$ , CL, and  $V_z$ . The concentration-time data will be summarized by descriptive statistics (n, mean, and standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time of the study. PK parameters will be estimated using a non-compartmental method with WinNonlin (Pharsight Corp, Cary, North Carolina). Individual serum concentration of versus actual day will be tabulated and plotted by dose level (linear and log scales). Plots of the mean or median concentrations of OsrHSA will be presented by nominal day (linear and log scale) by dose level. If 3 cohorts complete in the study, linearity in PK parameters will be tested by fitting the model:  $\log(C_{max} \text{ or } AUC) = a + b * \log(\text{dose}) + \text{Dose}$ . Dose-proportionality will be tested using Power Model.

A population PK-based modeling approach may also be applied for PK characterization and PK covariate analyses. The steady state PK profile may be projected based on the population PK model. Population PK and PD data may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between investigational drug exposure and biomarkers or significant safety endpoints. Alternative dosing approach, e.g., body size-based or fixed dosing, may be evaluated using a population PK/PD approach. The results of these analyses, if performed, will be reported separately.

### 11.4.2 Safety Analysis

Safety data will be summarized by treatment group using descriptive statistics. No formal inferential analyses are planned for safety comparisons. Continuous safety data will be summarized as sample size, mean, SD, minimum, and maximum, by scheduled time point and treatment for observed values and change from baseline values (as appropriate). Tabulations of frequencies and proportions, as appropriate will be used for the evaluation of categorical (qualitative) safety data.

Adverse events will be classified by SOC and term using the Medical Dictionary of Regulatory Activities (MedDRA) coding dictionary. Incidence of treatment-emergent adverse events (TEAEs) will be summarized by SOC and preferred term for each treatment group. Incidence of TEAEs will also be summarized by severity and association with the study treatments.

Concomitant medications will be presented in summary tables and listings.

All safety data summaries will be based on the Safety Analysis Set. No statistical tests will be performed for the safety endpoints.

Missing data will be treated as they are. No imputations of missing data are planned.

### **11.4.3 Immunogenicity Analysis**

All samples will first be analyzed for ADAs in a screening assay. Study samples with results below the screening cut-off will be reported as negative for ADAs. In the event of a positive result in the screening assay, samples will be analyzed in the confirmatory assay.

The incidence of ADA will be summarized for all subjects who received at least one administration of study drug. Impact of ADAs on PK, PD, and safety of the study drug will be evaluated, if applicable.

### **11.5 Tabulation of Individual Participation Data**

Data tabulations will summarize the following numbers of subjects:

- Enrolled
- Study drug treatment dose received
- Evaluable for safety
- Protocol violations
- Protocol completions
- Withdraw from study due to:
  - Adverse event
  - Physician's recommendation
  - Withdrew consent
  - Lost to Follow-up
  - Other reasons as collected on the eCRF

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