A phase I double-blind, placebo-controlled, randomized, single and multiple ascending dose finding study to evaluate the safety and pharmacokinetic profile of LSALT peptide in healthy participants

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Sponsor: Arch Biopartners Inc.

Study Site: Nucleus Network

Principal Investigator (PI): Dr. Ben Snyder

Protocol Approval Signatures

Protocol Title: A phase I double-blind, placebo-controlled, randomized, single and multiple ascending dose finding study to evaluate the safety and pharmacokinetic profile of LSALT Peptide in healthy participants

Protocol Number: AB001

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

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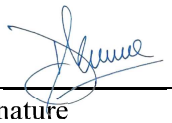

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1.0 SYNOPSIS

Inflammation resulting from infection or injury leads to tissue damage and eventually organ dysfunction/failure due to the effects of recruited immune cells. This process is regulated by many biological events which include the recruitment and adhesion of circulating leukocytes to endothelial cells prior to infiltration of the target tissue. Dipeptidase-1 is a common receptor that regulates the adhesion of circulating leukocytes to endothelial cells.

LSALT is a 16 amino acid peptide drug and a selective non-enzymatic dipeptidase-1 antagonist. LSALT peptide prevents leukocyte adhesion to endothelial cells creating numerous indications for targeting inflammation in the context of microbial and non-microbial (sterile) tissue injury. In pre-clinical mouse models, LSALT peptide has proven efficacious in preventing acute kidney injury induced by ischemia-reperfusion, toxins and sepsis. LSALT peptide has a favorable toxicology profile with little drug-related toxicity observed in animal studies. This is a first-in-human phase I clinical study to evaluate the safety and pharmacokinetics of single and multiple ascending doses of the LSALT peptide.

2.0 LIST OF ABBREVIATIONS

AKI	acute kidney injury
API	active pharmaceutical ingredient
ARDS	acute respiratory distress syndrome
DPEP-1	dipeptidase-1
GPI	glycosylphosphatidylinositol
IRI	ischemia reperfusion injury
IV	intravenous
LAL	limulus amebocyte lysate
LPS	lipopolysaccharide
MAD	multiple ascending dose
MTD	maximum tolerated dose
NOAEL	no observed adverse effect limit
PK	pharmacokinetics
SAD	single ascending dose
SRC	safety review committee

3.0 BACKGROUND AND RATIONALE

3.1 Inflammation and Organ Injury

Inflammation is a common pathway that contributes to the pathogenesis of many diseases caused by infection, allograft rejection, hypoxia, and autoimmunity. Although inflammation is regulated by many complex biological processes and can be activated by numerous microbial and non-microbial stimuli, a common framework of events exists regardless of disease context which includes activation of pattern recognition receptors, upregulation of pro-inflammatory cytokines, and recruitment of leukocytes to affected tissues[1-3]. The interactions between recruited leukocytes and endothelial cells has been studied in detail to understand the exact processes that allows immune cells to bind to and infiltrate into injured or infected tissues. Endothelial receptors for leukocyte adhesion

including various selectins (e.g. E-selectin), integrins and members of the immunoglobulin family (e.g. PECAM1) have been identified however other unknown receptors remain. Although inflammation is beneficial in eliminating microorganisms, abnormal and damaged cells during disease, it can also cause organ dysfunction and failure due to an excessive or unrelenting response that involves the overproduction of cytokines, cytotoxicity and cell death[4].

3.2 Acute Kidney Injury

Acute kidney injury is an example where excessive inflammation triggered by toxins or reduced renal blood flow results in organ failure. Acute kidney injury is a significant clinical problem for which no specific therapies, aside from supportive care, currently exist. Patients who experience acute kidney injury in several contexts are at higher risk of cardiovascular events, end-stage kidney disease and death[5].

1.2.1. Renal Ischemia Reperfusion Injury During Cardiac Surgery. Acute kidney injury (AKI) occurs in 30% of patients that undergo cardiac surgery with 1% of patients requiring dialysis[6]. Acute kidney injury represents an additional challenge in patients recovering from cardiac surgery as they have higher incidences of mortality, complications in treatment course, and higher risk of complications such as cardiovascular events and infection. Of the patients that require dialysis because of cardiac surgery-associated AKI, many will require lifelong dialysis which increases overall morbidity and mortality. During cardiac surgery, reduction in renal blood flow leads to ischemia and tissue injury in the kidney which triggers and inflammatory response. Recruited inflammatory cells adhere to activated endothelium leading to cellular injury and further pro-inflammatory responses ultimately causing further tissue injury and renal dysfunction. Even though renal inflammation is well documented as having a prominent role in cardiac surgery induced AKI[6], there is currently no specific therapies that target this condition. As an inhibitor of leukocyte activation/recruitment during inflammation, LSALT peptide is a novel therapeutic that may protect the kidneys from the consequences of ischemia and prevent AKI in patients undergoing cardiac surgery. This will be the first indication developed for LSALT peptide.

1.2.2. Sepsis-associated Acute Kidney Injury. Sepsis represents a systemic host inflammatory response to infection. Excessive inflammation leads to multi-organ dysfunction that includes acute kidney injury, shock liver and acute respiratory distress syndrome (ARDS)[7]. Incidence rates for severe sepsis is estimated at 50-300 per 100,000 population in the United States where half of those cases occur in the ICU[8,9]. Sepsis has a high rate of mortality where up to 50% of patients will have septic shock. Of the patients undergoing sepsis, it is estimated as many as 60% of those patients will develop sepsis-associated AKI with the elderly, women, and patients with co-morbidities such as chronic kidney disease, heart failure, or liver disease at higher risk. Similarly, liver dysfunction/failure can occur in up to 40% of patients with sepsis[10]. When sepsis affects the lung, 10% of septic patients can develop acute respiratory distress syndrome (ARDS) which is a life-threatening situation in which leaky blood vessels in the lungs compromise its ability to absorb oxygen[11]. This has downstream effects on many other organs due to the hypoxic injury that may occur due to the low oxygen environment. In septic patients that experience organ dysfunction, the incidence of morbidity and/or mortality is

significantly increased. Sepsis associated organ dysfunction is driven by a multi-faceted pathophysiological process including ischemic injury due to variations in hemodynamics, systemic cytokine-mediated inflammation, and subsequent cellular injury. The current standard of care aims to treat the underlying infection and provide physiologic support (such as mechanical ventilation and dialysis) for injured and failing organs. No specific therapy exists to protect the kidney and other organs from the deleterious effects of the inflammatory response and the associated long-term consequences (chronic kidney disease, chronic lung disease, etc). LSALT peptide provides a unique strategy to specifically block leukocyte recruitment and dampen the inflammatory response in these organs during sepsis which may preserve organ function and ameliorate long-term sepsis-associated morbidity and mortality.

1.2.3. Delayed Allograft Function and Kidney Transplantation. Ischemia reperfusion injury (IRI) is an unavoidable obstacle inherent to organ preservation and surgery during solid organ transplantation. As previously described, renal IRI results in a robust inflammatory response in the kidney through activation of an innate immune response. Research has shown delayed allograft function attributed to prolonged cold ischemia results in the loss of tubular cell mass and endothelial dysfunction in addition to enhanced graft immunogenicity[12]. Together, the ischemia-reperfusion injury associated with prolonged cold ischemia has a negative impact on both short- and long-term kidney allograft outcomes. Various therapies have been suggested including interfering with leukocyte adhesion which would reduce the level of inflammation in the allograft and prevent delayed graft function[13]. As a leukocyte adhesion inhibitor, LSALT peptide could provide protection against pro-inflammatory responses in the allograft either as an additive to the perfusion solution or given pre- and post-operatively to the recipient. This would prevent delayed allograft function and improve allograft survival.

1.2.4. Contrast-induced acute kidney injury (CI-AKI). CI-AKI occurs following the intravenous or intra-arterial administration of radiographic contrast agents for diagnostic imaging. Radiographic contrast is a known kidney toxin, and although the incidence rate of CI-AKI is low among patients with normal kidney function, patients with pre-existing kidney disease or heart failure have 2-3-fold increased risk[14-16]. Patients with CI-AKI experience a greater risk of cardiovascular events, chronic kidney disease requiring dialysis and mortality[14,15]. The incomplete understanding of the pathogenesis of CI-AKI has hampered the development of any effective strategies for the prevention of this complication. As above, pre-clinical studies have identified a substantial role for renal inflammation in the pathogenesis of CI-AKI. LSALT peptide represents a unique treatment strategy to prevent CI-AKI in high risk patients undergoing angiography procedures.

3.3 LSALT Peptide

LSALT is a peptide drug with the sequence NH3-LSALTPSPSWLKYKAL-COOH. LSALT peptide binds to DPEP-1 but does not inhibit its biologic enzymatic activity potentially minimizing off-target or other adverse effects. LSALT peptide inhibits leukocyte recruitment in multiple experimental disease models through the direct inhibition of leukocyte adhesion to DPEP-1. DPEP-1 represents a new molecular pathway for leukocyte

adhesion discovered by Arch scientists. Intellectual property and clinical development of LSALT peptide is currently assigned to Arch Biopartners Inc.

LSALT peptide was discovered by using an unbiased *in vivo* approach where a combinatorial phage display library[17] was used to isolate specific peptide-displaying-phage that homed to the liver and lungs of mice during an inflammatory condition. In brief, neutrophils were isolated from C57/BL6 mice. RNA isolated from these neutrophils were then converted into cDNA. These neutrophil derived cDNA's were then fused into the coat protein gene of T7 phage thereby generating a library called T7N. This resulted in a random pool of T7 phages which presented various neutrophil peptides on the surface. These phage display libraries were subtracted by depleting the phage that bound to background cells or primary murine unstimulated lung endothelium. Unbound phage were then isolated from the culture and injected into neutrophil-depleted mice after lipopolysaccharide (LPS) stimulation. Phage that bound to the lung and liver endothelium were recovered, isolated and re-injected into another group of mice to enrich for the specific homing phage. This process was repeated five times in vivo to identify enriched phage clones that specifically homed to the lungs and liver. After isolation, phage were screened on the basis of their ability to inhibit neutrophil recruitment in the liver sinusoids in the presence of LPS by intravital microscopy. A specific peptide-displaying phage was isolated that inhibited the adhesion of neutrophils in the liver sinusoids in response to LPS *in vivo*. This phage subclone expressed the peptide NH3-LSALTPSPSWLKYKAL-COOH and designated as LSALT peptide.

3.4 Pre-Clinical Data for Dipeptidase-I and LSALT Peptide in Acute Kidney Injury

1.4.1. DPEP-1 expression and function in kidney, liver, and lung. DPEP-1 expression and localization was characterized in renal tubular epithelial cells (TEC) cultured from human nephrectomy tissue samples were labeled with either zonula occludens-1 (ZO-1), a tight junction protein found on TEC, and DPEP-1. Confocal microscopy confirmed the expression of DPEP-1 on the surface of TEC. Additional characterization of DPEP-1 using immunohistochemical analysis revealed high expression levels in mouse kidney epithelium and endothelium as well as expression in lung and liver endothelium. Similar expression patterns have been confirmed in human lung, liver and kidney. Using immunoblotting, DPEP-1 expression was found in both total kidney lysates and isolated TEC which confirmed the microscopy findings. Although DPEP-1 is predicted to have a size of 42kDa, a 55kDa DPEP-1 protein was also detected due to the presence of a GPI anchor as well as post-translational glycosylation as demonstrated by the by the effects of PNGaseF. Functional activity of DPEP-1 was determined in various samples using fluorescent enzyme activity assay that demonstrated high levels of dipeptidase activity in both human and mouse kidney tissue.

1.4.2. Specificity of LSALT Peptide binding to DPEP-1. DPEP-1 as a binding target for LSALT peptide was confirmed by overexpressing rat, canine or human DPEP-1 in Cos-1 cells and treated with fluorescently labeled LSALT peptide. Analysis with fluorescent confocal microscopy of these cells demonstrated that LSALT peptide was bound only to cells expressing DPEP-1. This specific interaction was confirmed using a biotin-labeled LSALT peptide immunoprecipitation assay of DPEP-1. Total protein lysates from DPEP-1 overexpressing cells were treated with biotin-labeled LSALT peptide and the protein complex was pulled down with neutravidin conjugated beads before analysis by

immunoblotting using anti-DPEP-1 antibody. Immunoblot analysis revealed that DPEP-1 interacted with LSALT peptide but not non-specific control peptide indicating specificity of LSALT peptide binding to DPEP-1.

To ensure LSALT peptide would not target similar proteins, other members of the dipeptidase family were also assessed. Human DPEP-1, DPEP-2, and DPEP-3 were transiently expressed in Cos-1 cells before being treated with fluorescent-labeled LSALT peptide. Analysis by fluorescent microscopy revealed that LSALT peptide bound to DPEP-1 expressing cells but not DPEP-2 or DPEP-3 expressing cells.

DPEP-1 enzyme activity was tested using a fluorometric assay originally described by Heywood and Hooper in 1995[18]. Enzymatic activity of DPEP-1 was confirmed in lysates from human, rat, and mouse derived DPEP-1 expressing cells. Cilastatin or penicillamine, known functional inhibitors of DPEP-1, abrogated the enzymatic activity of both human and mouse DPEP-1. When cells expressing human DPEP-1 were treated with LSALT peptide, no significant decrease in DPEP-1 enzymatic activity was detected indicating that LSALT peptide binds to DPEP-1 but does not inhibit its enzymatic activity.

To determine whether the catalytic region of DPEP-1 was required for LSALT peptide interaction, a catalytically inert human DPEP-1 (E141D) was transiently expressed in Cos-1 cells and treated with fluorescent LSALT peptide. Analysis by fluorescent microscopy demonstrated removal of catalytic activity had no effect on LSALT peptide binding on cells as compared to normal DPEP-1 or negative mutant control (H215). Loss of enzymatic activity in the catalytically inert DPEP-1 (E>D) was confirmed using the fluorometric assay[13]. Protein expression level of catalytically inert DPEP-1 (E141D) in Cos-1 cells was also confirmed by immunoblotting.

In a human *in vitro* static neutrophil adhesion assay, LSALT peptide inhibited neutrophil adhesion to activated endothelium at concentrations as low 1 μg/ml.

1.4.3. DPEP-1 plays a role in renal ischemia reperfusion injury. Renal ischemia/reperfusion injury (IRI) is a major cause of acute kidney injury (AKI). A reduction in renal blood flow followed by reperfusion during patient recovery occurs in numerous clinical contexts including cardiac surgery and kidney transplantation. Renal IRI results in inflammation that includes leukocyte infiltration, renal hemorrhage, and tubular cell necrosis. Inflammation plays a significant role in the pathophysiology of renal IRI, however there are currently no therapeutic strategies in human AKI that directly target this pathway. To determine the potential impact of LSALT peptide in renal IRI, a survival model of murine renal IRI was employed where a vascular clamp is placed on the renal pedicle of a unilateral nephrectomised mouse to induce warm ischemia and subsequently released to induce reperfusion injury. A significant inflammatory response can be observed in the kidney as early as 2 hours of renal IRI with large numbers of monocytes and neutrophils infiltrating into the tubular/interstitial space. Furthermore, because of immune cell infiltration and extravasation, loss of endothelial integrity can also be observed as blood vessels become leaky and no longer retain their web-like organization.

Phenotypically, mice undergoing renal IRI developed oliguria/anuria over the course of 2 days due to loss of kidney function measured as an increase in serum creatinine. Treatment

of mice with LSALT peptide (10 µg/kg) prior to renal IRI ameliorated AKI allowing mice to maintain normal urine output and preserving renal function. A similar effect on acute kidney injury was also seen with cilastatin (35 µg/kg), a chemical inhibitor of DPEP-1, albeit less effective than LSALT peptide. Furthermore, dose response experiments demonstrated that LSALT peptide effectively inhibited the inflammatory response to renal IRI at a dose as low as 100ng/kg.

Use of another DPEP-1 targeting peptide, GFE-1[17] (10 µg/kg), also demonstrated protection against renal IRI induced inflammation in a similar manner as LSALT peptide (10 µg/kg).

1.4.4. DPEP-1 is a key molecule in contrast induced acute kidney injury. Radiographic contrast agents for diagnostic imaging are renal toxins that can induce acute kidney injury (CI-AKI). Inflammation plays a major role in the pathogenesis of CI-AKI. To determine if DPEP-1 inhibition using LSALT peptide or cilastatin could protect against CI-AKI, a mouse model was employed. Mice were volume depleted by water deprivation for 48 hours to induce pre-renal azotemia. Mice were then administered intravenous iodinated contrast agent (ioversol) and followed for 72 hours. In untreated mice, intravital microscopy revealed the recruitment of inflammatory monocytes and neutrophils at 6h resulting in tissue damage and AKI by day 3. Treatment with LSALT peptide (10 µg/kg) and cilastatin (35 µg/kg) prior to contrast administration reduced renal inflammation at 6 hours. Phenotypic studies demonstrated that mice treated with contrast agent developed anuria/oliguria over the course of 3 days and impaired renal function reflected by increased serum creatinine while LSALT peptide and cilastatin preserved urine output and prevented AKI in mice receiving ioversol at 3 days. LSALT peptide and cilastatin administered together did not provide any additive benefit.

3.5 Drug Metabolism and Pharmacokinetics

Plasma levels of LSALT peptide were measured post-intravenous dosing of 100, 250 and 450 mg/kg in rats. Terminal elimination half-lives of 0.66 – 1.17 hr and MRT_{obs} values of 0.58 – 0.85 hr were observed for LSALT peptide. The $AUC_{0-\infty}$ was linear and close to proportional with dose.

LSALT peptide is stable in human plasma for up to 90 minutes with no detectable metabolic/proteolytic fragments as measured by mass spectrometry. LSALT peptide is undetectable in whole blood in the absence of phosphoric acid due to red or white blood cell binding. In human whole blood, 90% or more of the LSALT peptide is contained within the cellular compartment. LSALT peptide however is compatible with blood and does not induce red blood cell hemolysis. Work is ongoing to identify LSALT peptide volume of distribution, tissue biodistribution, and excretion.

3.6 Toxicology and Safety

The maximum tolerated dose (MTD) of LSALT peptide in mice and rats is 100 and 450 mg/kg respectively, several logs above the minimum effective dose of 100 ng/kg to prevent kidney inflammation and injury in mice. In dogs, the MTD of LSALT is 20 mg/kg. In all mouse studies, no LSALT peptide-related toxicity has been observed at therapeutic doses.

3.6.1 14-Day Toxicology Studies

Rats: A GLP study assessed the potential toxicity and toxicokinetics of LSALT peptide when administered by intravenous injection to Sprague-Dawley rats once daily for 14 days. Three dose groups of 10, 30 and 50 mg/kg were evaluated. The control group was administered the vehicle used to prepare the LSALT peptide dosing formulations (0.9% sodium chloride, USP). The LSALT Peptide dose formulations and the control vehicle were administered to rats by intravenous bolus injection at a dose volume of 1 mL/kg based on the animal's most recently scheduled body weight. The progression or regression of any effects was evaluated during an additional 14-day treatment-free, recovery period in the control and high dose groups.

Male and female rats [strain: Crl: CD® (SD) BR-Sprague-Dawley; Charles River] were acclimated for this study for 16 days. During the acclimation period, observations for clinical signs and ophthalmology were conducted and body weights as well as food consumption were measured. Following the pre-study evaluations, rats were randomized by body weight to control and test groups.

There were no statistically significant differences in body weight, body weight changes, or food consumption between the treated and control groups during the study.

There were no ophthalmological or neurological findings considered to be related to treatment with the test item.

Changes in hematology and clinical chemistry were mild, generally within normal ranges, and unlikely of clinical significance.

There were no gross findings that could be related to the test item treatment. There were no statistically significant findings on organ weights that could be attributed to the test item treatment

LSALT Peptide administered to Sprague-Dawley rats by intravenous bolus administration daily, for 14 days in the dose range of 10 to 50 mg/kg was well tolerated with no test-item related effects observed upon evaluation of clinical observations, body weights, food consumption, clinical pathology (chemistry/hematology), gross pathology or histopathology. The NOAEL in rats is 50 mg/kg.

Dogs: A GLP study assessed the potential toxicity and toxicokinetics of LSALT Peptide when administered by intravenous infusion to Beagle dogs once daily for 14 days. The control group was administered the vehicle used to prepare the LSALT Peptide dosing formulations (0.9% sodium chloride, USP). Three dose groups of 2.5, 7.5 and 15 mg/kg were evaluated. The LSALT peptide dose formulation and the control vehicle were administered to animals by intravenous infusion at a dose volume of 2 mL/kg based on the animal's most recently scheduled body weight. The progression or regression of any effects was evaluated during an additional 14-day treatment-free, recovery period in the control and high dose groups.

LSALT peptide administered to Beagle dogs by intravenous infusion administration daily, for 14 days in the dose range of 2.5 to 7.5 mg/kg was well tolerated with no test-item related clinical observations noted. The dose level of 15 mg/kg resulted in manifestation of pseudo-allergic (anaphylactoid) reactions[1]. The clinical signs appeared shortly after dosing and consisted of reddening of the skin around the eyes and mouth, head flicking, facial edema, hives/reddening on the pinnae, and/or reddened eyes and muzzle. Pseudo-allergic reactions were typically observed throughout the entire treatment phase duration. Affected animals were treated with diphenhydramine by IV injection. These reactions occurred during infusion and disappeared shortly after the infusion was completed. Other clinical signs were sporadic and were not considered to be related to treatment with the test item. Thereactions may likely diminish by increasing the time of infusion for delivering dose levels more than 15 mg/kg.

Pseudo-allergic reactions following intravenous administration of peptide/proteins in dogs have been reported and occur in response to the infusion of biotherapeutics. Non-clinical infusion reactions do not predict responses in humans[19-21]. .

Repeated dosing in the dose range of 2.5 to 15 mg/kg had no statistically significant effects. There were no differences in vital signs, body weight, or food consumption between the treated and control groups during the study. Changes in hematology and clinical chemistry were mild, generally within normal ranges, and unlikely of clinical significance. No changes in gross pathology and histopathology were attributed to the test item. Gross findings noted upon necropsy of Main Study animals included a white-tan area of capsular thickening and contraction in the spleen of one mid dose female and marked enlargement, redness, and protrusion of the right third eyelid in the eye of one high dose female. These gross findings were considered incidental and unlikely to be test item related. There were no statistically significant findings on organ weights that could be attributed to the test item treatment.

The NOAEL in dogs is 2.5 mg/kg.

3.7 Preliminary Safety in Humans

The first 6 cohorts of this study have been completed including subjects receiving a single 5 mg dose. No significant adverse effects were reported in any subjects receiving a single or multiple doses of the LSALT peptide.

3.8 Study Rationale

Acute kidney injury is a devastating complication for patients undergoing surgery, diagnostic imaging or in the context of critical illness. Currently there are no effective therapies to prevent or minimize acute kidney injury. Inflammation is an important factor

[1] An allergic reaction is marked by the activation of the immune system by an allergen and includes signs that involve the skin, nose/throat, upper airway, GI tract, lungs and cardiovascular system. While the animals exhibited clinical features that would be seen in an allergic reaction, given its self-limited nature and severity, and the fact that they occurred only during the infusion, the findings are considered to represent a non-immune infusion reaction. Thus, the effects were considered pseudo-allergic or anaphylactoid.

in the pathogenesis of acute kidney injury. Given its favorable initial toxicology profile, the administration of LSALT peptide to target inflammation and prevent acute kidney injury has the potential to provide a significant clinical impact. Since LSALT peptide is a new drug, this phase I study to evaluate safety and pharmacokinetics is the first step needed to advance the LSALT peptide for the prevention of acute kidney injury in humans.

A third MAD cohort of 5 mg administered intravenously daily for 3 days is being proposed to obtain additional pharmacokinetic data.

4.0 OBJECTIVES

4.1 Primary Objective

To determine the safety and tolerability of 4 single and multiple ascending doses of LSALT peptide in healthy participants.

4.2 Secondary Objective

To evaluate the pharmacokinetics and pharmacodynamics of LSALT peptide in healthy participants

5.0 STUDY DESIGN

This is a double-blind, placebo-controlled, randomized, adaptive design single and multiple ascending dose study to evaluate the safety and pharmacokinetics of LSALT peptide in healthy participants.

To establish a safe starting dose of LSALT peptide, unblinded low dose escalation will first be performed in a small cohort of participants. 0.01 mg of LSALT peptide will be administered intravenously (IV) once. If no adverse effects are observed following 72 hours, subsequent single (n=1) participants will be administered escalating doses of 0.1 mg, 0.3 mg and 0.5mg every 72 hours. If no adverse effects are observed at the 0.5 mg dose, then the study will proceed to the first cohort of 8 participants (6 active treatment, 2 placebo per dose level) who will receive 1.0 mg of LSALT peptide in a double-blinded fashion. Safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) will be assessed before escalating to the next cohort. Dosing will be completed in two sequential cohorts of 8 participants using doses of 2.5 mg and 5.0 mg. The first 2 participants in each blinded cohort will act as sentinels (1 treatment, 1 placebo) who must show no adverse effects before continuing the study under the current design.

Once safety, PK and PD data are completed in the single ascending dose cohort, and the LSALT peptide is determined to be safe and well-tolerated by the Safety Review Committee (SRC), the multiple ascending dose arm of the study will proceed. The multiple ascending dose arm will consist of 2 cohorts of 8 participants receiving 2 independent doses of the LSALT peptide or placebo once or twice daily for 3 consecutive days. The doses for this arm of the study will consist of the 2 highest doses determined by the SRC to be safe in the SAD cohort. The first cohort will receive drug in a double-blinded fashion. Safety, tolerability, PK, and PD will be assessed before escalating to the next cohort. Each cohort will consist of 6 active treatment, 2 placebo per dose

level. The first 2 participants in each cohort will act as sentinels (1 treatment, 1 placebo) who must show no adverse effects before continuing the study under the current design.

6.0 PATIENT SELECTION

6.1 Inclusion Criteria

1. Adult participants aged 18-55 years (inclusive at the time of screening).
2. No prior history of major organ or systemic disease including diabetes, hypertension, kidney, heart or liver disease. Participants with childhood asthma are acceptable.
3. Normal hematology, clinical chemistry and urinalysis parameters at screening, unless not deemed clinically significant by the investigator.
4. Body Mass Index (BMI) between 18 kg/m^2 and 32 kg/m^2 (inclusive)
5. Taking no prescription medications 2 weeks prior to admission or over-the-counter medications 7 days prior to admission. Occasional use of paracetamol or ibuprofen (up to 1000 mg and 400 mg/day respectively) are acceptable. Routine vitamins and supplements are permissible at the discretion of the investigator.
6. Able to allow intravenous medication to be administered.
7. Males (along with their female partners) and females of childbearing potential (defined as a female who is not menopausal or surgically sterilized) must be willing to use an acceptable method of birth control during heterosexual activities including a condom and a second highly effective method (i.e., hormonal contraceptive, intra-uterine device) or abstinence for the duration of the study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Males and females should continue with the aforementioned contraception for 90 days after the last dose.
8. Able to understand and willing to sign an ethics committee-approved written informed consent document
9. Non-smokers. Social and light smokers of up to 10 cigarettes per day who can abstain from smoking during the confinement period and have no evidence of underlying lung disease (bronchitis, COPD or reactive airways disease).
10. Willing to remain abstinent from alcohol 24 hours prior to admission and until after the confinement period in the unit.

6.2 Exclusion Criteria

1. A history of cardiovascular disease, diabetes or hypertension (Screening assessment >150/90 after 5 minutes sitting), significant neurological, pulmonary (including asthma), hepatic, rheumatic, autoimmune, haematological, metabolic or renal disorder.
2. Prescription medications are prohibited. No prescription medications 2 weeks prior to admission or over-the-counter medications 7 days prior to admission. Occasional use of paracetamol or ibuprofen (up to 1000 mg and 400 mg/day respectively) are acceptable. Routine vitamins and supplements are permissible at the discretion of the investigator
3. Any moderate or severe allergies, including anaphylaxis, to food, drugs or environmental allergens. Mild allergies such as hayfever may be included.
4. Females who are pregnant or lactating. Women of childbearing potential must have a negative pregnancy test within 14 days of study initiation and at baseline.

5. Consumption of caffeine 48 hours prior to start of study treatment and whilst confined to the unit.
6. History of any psychiatric illness or psychological disorder which may impair the ability to provide written informed consent or participate in the study
7. Clinically significant abnormal laboratory value at screening as determined by the Investigator.
8. Participant is sero-positive to HIV-1 or HIV-2, HCV or HBV.
9. History or presence of alcoholism within two years prior to the first study drug administration or drugs of abuse unless it can be explained to the satisfaction of the investigator that it is due to a standard dose of a prescribed medication and that an adequate wash-out will occur prior to admission as per inclusion #5
10. No findings on clinical examination that, in the opinion of the investigator, could compromise the safety of the participant or the results of the study.
11. Blood donation or significant blood loss within 60 days prior to the first study drug administration.
12. Administration of investigational product in another trial within 30 days prior to the first study drug administration or five half-lives, whichever is longer.
13. Surgery within the past 3 months prior to the first study drug administration determined by the PI to be clinically relevant.
14. Active malignancy or history of malignancy in the past 5 years

6.3 Enrollment and Randomization

52 participants will be enrolled in the study. 8 participants will be randomly selected to a substitution list to be used in the event of drop-out. Block randomization method will be used for remaining participants with a sample number of 8/group and a 3:1 treatment:placebo ratio. A Randomization Plan will be created, and the randomization of eligible study participants will be managed as per the plan. A Randomization and Substitution List will be prepared using a statistical software package.

6.4 Blinding

Participants and the study investigators/personnel will be blinded. This is a third-party blinded study whereupon the pharmacist (or designate) preparing the LSALT peptide or placebo for infusion will be unblinded.

6.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

7.0 STUDY PROCEDURES

This single center study is a double-blind, placebo-controlled, randomized, single and multiple ascending dose phase I study of LSALT peptide safety, tolerability, and pharmacokinetics.

7.1 Single Ascending Dose (SAD) Cohort

7.1.1 Sample Size. The study sample size will be 4 + 24 participants for the SAD arm of the protocol. The first 4 participants will comprise a low dose escalation cohort, and 3 cohorts of 8 (6 treatment and 2 placebo) will comprise the single ascending dose cohorts.

7.1.2 LSALT Peptide Dosing. It is anticipated that seven single intravenous doses of LSALT peptide (0.01 mg, 0.1 mg, 0.3 mg, 0.5 mg, 1 mg, 2.5 mg and 5 mg) will be administered in this arm of the study.

The first 4 participants will each sequentially receive a single escalating low dose of the LSALT peptide (0.01 mg, 0.1 mg, 0.3 mg or 0.5 mg). Escalation to the next dose and participant will occur every 72 hours if no adverse effects are seen. Participants will then be enrolled in cohorts of 8 and randomized to treatment or placebo in a 3:1 ratio. The dose for the first SAD cohort will be 1 mg administered intravenously once over 2 hours. The first 2 subjects of each cohort will be sentinels (1 treatment, 1 placebo). Continuation of the study in each cohort will occur if no clinical or biochemical adverse effects are observed in the sentinels as determined by the Safety Review Committee (SRC). Escalation to the higher dose cohorts (2.5 mg and 5 mg) will occur after 10-14 days if no clinical or biochemical adverse effects are observed in the prior cohort.

A rationale for the proposed doses is based on the NOAEL in dogs (2.5 mg/kg) and the minimum effective dose in mice (0.1-1 μg/kg). The human equivalent dose is 1.4 mg/kg. The 1 mg dose (16.7 μg/kg in a 60 kg human) is 1200-fold less than the maximum tolerated dose of 20 mg/kg in dogs, 150-fold lower than the NOAEL and provides a safety factor of 83 relative to the calculated human equivalent dose. The 5 mg dose (83.3 mcg/kg in a 60 kg human) is 240-fold less than the maximum tolerated dose of 20 mg/kg in dogs, 30-fold less than the NOAEL and provides a safety factor of 17 relative to the calculated human equivalent dose. Based on the minimum therapeutic dose observed in mice (0.1 - 1 μg/kg), a conservative first dose of 0.01 mg (166.7 ng/kg in a 60 kg human) is chosen to further increase the safety margin of the starting dose by 100-fold (i.e. 8400 x less than the human equivalent dose calculated from the NOAEL).

7.1.3 Confinement. Participants will be confined for 24 hours following infusion of the LSALT peptide or placebo.

7.1.4 SAD Study Procedures

- **Day -29. Pretreatment Evaluation and Randomization.** 28 days prior to study initiation, enrolled participants will undergo informed consent, followed by a complete history and physical examination (including body weight and height) including seated vital signs (temperature, Blood Pressure, pulse oximetry Respiratory rate and Heart Rate), drugs of abuse and an alcohol breath test, baseline fasting laboratory studies (CBC, clinical chemistry), Coagulation profile (INR and PTT), urinalysis, 12-lead electrocardiogram (Supine) and chest x-ray (Single PA view). Women of child-bearing age will have a β-hCG to rule out pregnancy. Participants will then be randomized.

Low dose cohort

- **Day -1 Admission.** Participant 1 will undergo a clinical evaluation including vital signs, complete physical examination (including body weight and height), 12-lead

electrocardiogram, drugs of abuse and alcohol breath test, urinalyses, 25 ml of blood drawn for safety laboratory investigations including CBC, clinical chemistries, Coagulation profile (INR and PTT), and women of child-bearing age will have urine pregnancy test to rule out pregnancy.

- **Day 1. First Dose.** Participant 1 will undergo a clinical evaluation including vital signs. Participant 1 receives a single infusion of the LSALT peptide, 0.01 mg administered over 2 hours. Clinical evaluation, including vital signs, symptom directed physical examination, 12-lead electrocardiogram and 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries and coagulation profile (INR and PTT), 24 hours post the end of infusion. If the participant shows no adverse events, they will be discharged from the unit on Day 2.
- **Day 4. Follow up.** Participant 1 returns for an outpatient follow up visit. Adverse events are recorded, clinical evaluation including vital signs, complete physical examination, urinalyses, 12-lead electrocardiogram and 25 ml of blood drawn for safety laboratory investigations including coagulation profile (INR and PTT),
- **Day 4. Admission.** Participant 2 will undergo a clinical evaluation including vital signs, complete physical examination, 12-lead electrocardiogram, drugs of abuse and alcohol breath test, urinalysis, 25 ml of blood drawn for safety laboratory investigations including CBC, clinical chemistries, coagulation profile (INR and PTT) and women of child-bearing age will have a urine pregnancy test to rule out pregnancy.
- **Day 5. Dose escalation.** Participant 2 will undergo a clinical evaluation including vital signs. Participant 2 receives a single infusion of the LSALT peptide, 0.1 mg administered intravenously over 2 hours. Clinical evaluation, including vital signs, symptom directed physical examination, 12-lead electrocardiogram ,and 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries and coagulation profile (INR and PTT) 24 hours post the end of infusion. If the participant shows no adverse events, they will be discharged from the unit on Day 6.
- **Day 8. Follow up** Participant 2 returns for an outpatient follow up visit. Adverse events are recorded, clinical evaluation including vital signs, a complete physical examination, urinalyses, 12-lead electrocardiogram and 25 ml of blood drawn for safety laboratory investigations including coagulation profile (INR and PTT).
- **Day 8 Admission:** Participant 3 will undergo a clinical evaluation including vital signs, complete physical examination, 12-lead electrocardiogram, drugs of abuse and alcohol breath test, urinalyses, 25 ml of blood drawn for safety laboratory investigations including CBC, clinical chemistries and coagulation profile (INR and PTT) and women of child-bearing age will have a urine pregnancy to rule out pregnancy.
- **Day 9. Dose escalation.** Participant 3 will undergo a clinical evaluation including vital signs. Participant 3 receives a single infusion of the LSALT peptide, 0.3 mg administered intravenously over 2 hours. Clinical evaluation, including vital signs, symptom directed physical examination, 12-lead electrocardiogram and 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries and coagulation profile (INR and PTT) 24 hours post the end of infusion. If the participant shows no adverse events, they will be discharged from the unit on Day 10.
- **Day 12 Follow up:** Participant 3 returns for an outpatient follow up visit. Adverse events are recorded, clinical evaluation including vital signs, complete physical examination, urinalyses, 12-lead electrocardiogram and 25 ml of blood drawn for safety laboratory investigations including coagulation profile (INR and PTT).

- **Day 12 Admission:** Participant 4 will undergo a clinical evaluation including vital signs, complete physical examination, 12-lead electrocardiogram, drugs of abuse and alcohol breath test, urinalyses, 25 ml of blood drawn for safety laboratory investigations including CBC, clinical chemistries, coagulation profile (INR and PTT) and women of child-bearing age will have a urine pregnancy test to rule out pregnancy.
- **Day 13. Dose escalation.** Participant 4 will undergo a clinical evaluation including vital signs. Participant 4 receives a single infusion of the LSALT peptide, 0.5 mg administered intravenously over 2 hours. Clinical evaluation, including vital signs, symptom directed physical examination, 12-lead electrocardiogram and 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries, coagulation profile (INR and PTT) 24 hours post the end of infusion. If the participant shows no adverse events, they will be discharged from the unit on Day 14
- **Day 16 Follow up.** Participant 4 returns for an outpatient follow up visit. Adverse events are recorded, clinical evaluation including vital signs, complete physical examination, urinalyses, 12-lead electrocardiogram and 25 ml of blood drawn for safety laboratory investigations including coagulation profile (INR and PTT).

Treatment and Assessment Timetable (Low Dose)

Participant		1				2				3				4			
Study Day	Screening -29 to -2	-1	1	2	4	4	5	6	8	8	9	10	12	12	13	14	16
In patient period		X	X			X	X			X	X			X	X		
Informed consent	X																
Vital signs	X	X	X[1]	X	X	X	X[1]	X	X	X	X[1]	X	X	X	X[1]	X	X
Physical Exam	X	X		X	X	X		X	X	X		X	X	X		X	X
Alcohol Breath test	X	X				X				X				X			
Drugs of Abuse	X	X				X				X				X			
Urinalysis	X	X		x	X	X		x	X	X		x	X	X		x	X
CBC	X	X		X	X	X		X	X	X		X	X	X		X	X
Chemistry	X	X		X	X	X		X	X	X		X	X	X		X	X
Creatinine/eGFR	X	X		X	X	X		X	X	X		X	X	X		X	X
LFTs	X	X		X	X	X		X	X	X		X	X	X		X	X
INR/PTT	X	X		X	X	X		X	X	X		X	X	X		X	X
CXR	X																
ECG	X	X	X[2]		X	X	X[2]		X	X	X[2]		X	X	X[2]		X
B-hCG[3]	X	X			X	X			X	X			X	X			X
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LSALT Administration			X				X				X				X		
Discharge from unit				X				X				X				X	
Follow up					X				X				X				X

Note: Fasting for blood sampling required for Screening and post dose Follow up. Participants will be required to have fasted from all food and drink except water for at least 8 hours prior to blood sampling .

1. Vital signs dosing day (seated): pre dose (+/-30 mins), 1 hour (+/- 10mins), 2 hour (+/- 10 mins) 6 hours (+/- 15min) and 10 hours post completion of infusion (+/- 30 mins).
2. 12 lead electrocardiogram (supine): pre dose (+/- 30 mins), 2 hours (+/- 15 mins) and 8 hours post completion of infusion (+/- 30 mins)
3. Pregnancy test will be via serum B-hCG at Screening and a urine pregnancy test at pre dose (Study Day -1, Day 4, Day 8, Day 12) and follow up.

SAD Cohorts

- **Day -1**. Admission to unit; Participants will undergo a clinical evaluation including complete vital signs and physical examination, 12-lead electrocardiogram (supine), drugs of abuse and alcohol breath test, urinalyses and 25 ml of blood drawn for safety

laboratory investigations including CBC, clinical chemistries, coagulation profile (INR and PTT) and women of child-bearing age will have a urine pregnancy test to rule out pregnancy.

- **Day 1. Cohort 1.** Participants will undergo a clinical evaluation, including vital signs and 12-lead electrocardiogram .5 ml of blood will be drawn at 30 prior to LSALT peptide infusion for baseline PK measurements. LSALT peptide infusion will begin and run over 2 hours. 5 ml of blood will be drawn at 15 minutess, 30 minutes, 1, 2, 4, 6, 8, and 12 hours after the LSALT infusion has started.
- **Day 2.** Participants will undergo a clinical evaluation, including vital signs and symptom directed physical examination. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries, coagulation profile (INR and PTT) and 24 hour PK sample. An ECG will also be completed. If the participant shows no adverse events, they will be discharged from the unit.
- **Day 4.** Participants will undergo a clinical evaluation, including vital signs and a symptom directed physical examination. 25 ml of blood will be drawn for laboratory investigations, including 72 hour PK sample. An ECG will also be completed.
- **Day 7.** Participants will return for a clinical evaluation, including vital signs and a complete physical examination. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries and PK. A urinalysis, CXR and ECG will also be completed. Women of child-bearing age will have a urine pregnancy test to rule out pregnancy
- **Day 14. Cohort 2.** Conducted as per Cohort 1 to day 7.
- **Day 28. Cohort 3.** Conducted as per Cohort 1 to day 7.

Treatment and Assessment Timetable (SAD)

Study Day	Screen -29 to -2	-1	1	2	4	7
In patient period		X	X			
Informed consent	X					
Vital signs	X	X	X[4]	X	X	X
Physical Exam	X	X		X	X	X
Alcohol Breath Test	X	X				
Drugs of Abuse[6]	X	X				
Urinalysis	X	X		x		X
CBC	X	X		X		X
Chemistry	X	X		X		X
Creatine/eGFR	X	X		X		X
LFTs	X	X		X		X
PK			X[1]	X[2]	X[3]	X
INR/PTT	X			X		
CXR	X					X
ECG	X	X	X[5]	X	X	X
B-hCG[7]	X	X				X
Adverse Event	X	X	X	X	X	X
LSALT Administration			X			
Discharge from unit				X		
Follow up					X	X

Note: Fasting for blood sampling required for Screening and post dose Follow up. Participants will be required to have fasted from all food and drink except water for at least 8 hours prior to blood sampling.

1. PK blood samples: 5 ml of blood will be drawn at 30 mins pre (+/- 5 mins) and 15 mins (+/- 5 mins), 30 mins (+/- 5 mins), 45 mins (+/- 5 mins), 1h (+/- 5 mins), 2h (+/- 5 mins), 4h (+/- 10 mins), 6h (+/- 10 mins), 8h (+/- 10 mins), and 12h (+/- 30 mins) after the LSALT infusion has completed
2. PK blood sample: 24 hours (+/- 30 mins) after infusion has completed
3. PK blood sample: 72 hours (+/- 30 mins) after Infusion has completed

4. Vital signs dosing day (seated): pre dose within 30 mins prior to infusion start), 1 hour (+/- 10mins), 2 hour (+/- 10 mins) 6 hours (+/- 15min) and 10 hours post completion of infusion (+/- 30 mins)
5. 12 lead electrocardiogram (supine): pre dose (+/- 30 mins), 2 hours (+/- 15 mins) and 8 hours post completion of infusion (+/- 30 mins)
6. Repeat Drugs of Abuse (DoA) is permitted at the discretion of the Investigator
7. Pregnancy test will be via serum B-hCG at Screening and a urine pregnancy test at pre dose (Study Day -1Day 12) and follow up

7.2 Multiple Ascending Dose (MAD) Cohort

7.2.1 Sample Size. The study sample size will be 24 for the MAD arm of the protocol in cohorts of 8. Participants will be randomized to treatment or placebo in a 3:1 ratio. The first 2 subjects of each cohort will be sentinels (1 treatment, 1 placebo). Continuation of the study in each cohort will occur if no clinical or biochemical adverse effects are observed in the sentinels as determined by the Safety Review Committee (SRC). Escalation to the higher dose will occur if no clinical or biochemical adverse effects are observed after a 10 day follow-up period as determined by the SRC.

7.2.2 LSALT Peptide Dosing. The doses for the MAD cohorts will be determined by the SRC based on the results from the prior SAD and MAD arms of the study. These doses have been determined to be 1 mg, 2.5 mg and 5 mg. LSALT peptide will administered intravenously once daily for 3 days. The starting dose for the Phase 1 clinical study will be subject to change and reassessed based on the results from the SAD cohort and in accordance with FDAs guidance document for estimating a safe starting dose in initial clinical trials.

7.2.3 Confinement. Participants will be confined for days -1 to day 4 during the administration of the LASLT peptide.

7.2.4 Replacement. In the event of participant drop-out, participants from the reserve pool will be enrolled in the study and randomized.

7.2.5 MAD Study Procedures

- **Day -29. Pretreatment Evaluation and Randomization.** 29 days prior to study initiation, enrolled participants will undergo informed consent, followed by a complete history and physical examination (including body weight and height) vital signs (seated), alcohol breath test, drugs of abuse test, baseline fasting laboratory studies (CBC, clinical chemistry) including coagulation profile (INR and PTT), urinalysis, 12-lead, electrocardiogram (supine) and chest x-ray (single PA view). Women of child-bearing age will have a β-hCG to rule out pregnancy. Participants will then be randomized.
- **Day -1**. Admission to unit. Participants will undergo a clinical evaluation including complete vital signs and physical examination, 12-lead electrocardiogram (supine), drugs of abuse and alcohol breath test, urinalyses, 25 ml of blood drawn for safety laboratory investigations including CBC, clinical chemistries, urinalysis and women of child-bearing age will have a urine pregnancy test to rule out pregnancy.
- **Day 1.** Participants will undergo clinical evaluation including vital signs. 5 ml of blood will be drawn at 30 minutes prior to LSALT peptide infusion for baseline PK measurements. LSALT peptide infusion will begin and run over 2 hours. 5 ml of blood will be drawn at 15, 30, 45 60, 75, 90, 105, 120, 125, 130, 135, 140 minutes, and 3 hours from the onset of the LSALT infusion.

- **Day 2.** Participants will undergo a clinical evaluation, including vital signs, a brief history and symptom directed physical exam. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries and coagulation profile (INR and PTT), urinalysis and 24 hour PK sample (from the onset of the first LSALT infusion). An ECG will also be completed. If the participant shows no adverse events, they will receive the second dose of the LSALT peptide.
- **Day 3.** Participants will undergo a clinical evaluation, including vital signs, a brief history and a symptom directed physical exam. If the participant shows no adverse events, they will receive the third dose of the LSALT peptide. 5 ml of blood will be drawn at 15, 30, 45 60, 75, 90, 105, 120, 125, 130, 135, 140 minutes, and 3 hours from the onset of the LSALT infusion.
- **Day 4.** Participants will undergo a clinical evaluation, including vital signs and a symptom directed physical examination. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries, coagulation profile (INR and PTT) and a 72 hour PK sample (from the onset of the first LSALT infusion). A urinalysis, CXR and ECG will also be completed. If the participant shows no adverse events, they will be discharged from the unit.
- **Day 7.** Participants will return for a clinical evaluation, including a brief history, vital signs and a symptom directed physical examination. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries, coagulation profile (INR and PTT) and a 96 hour PK sample (from the end of the 3rd LSALT infusion). A urinalysis will also be completed.
- **Day 14.** Participants will return for a clinical evaluation, including a brief history, vital signs and symptom directed physical examination. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries. A urinalysis will also be completed and a sample of blood drawn for anti-drug antibodies.
- **Day 21.** Participants will return for a clinical evaluation, including a brief history, vital signs and a complete physical examination. 25 ml of blood will be drawn for laboratory investigations, including CBC, clinical chemistries. A urinalysis and ECG will also be completed. Women of child-bearing age will also have a urine pregnancy test
- **Day 28.** Begin Cohort 2 or 3**.** Conducted as per Cohort 1 to day 21.

Treatment and Assessment Timetable (MAD)

Study Day	Screen -29 to -2	-1	1	2	3	4	7	14	21
In patient period		X	X	X	X				
Informed consent	X								
Vital signs	X	X	X[6]	X[6]	X[6]	X	X	X	X
Physical Examination	X	X		X	X	X	X	X	X
Alcohol Breath Test	X	X							
Drugs of Abuse	X	X							
Urinalysis	X	X		X		X	X	X	X
CBC	X	X		X		X	X	X	X
Chemistry	X	X		X		X	X	X	X
Creatinine/eGFR	X	X		X		X	X	X	X
LFTs	X	X		X		X	X	X	X
PK			X[1]	X[2]	X[3]	X[4]	X[5]		
INR/PTT	X			X		X	X		
CXR	X					X			
ECG	X	X	X[7]	X[7]	X[7]	X			X

B-hCG[8]	X	X							X
Adverse Event	X		X	X	X	X	X	X	X
Anti-Drug Antibodies								X	
LSALT Administration			X	X	X				
Discharge from unit						X			
Follow up							X	X	X

Note: Fasting for blood sampling required for Screening and post dose Follow up. Participants will be required to have fasted from all food and drink except water for at least 8 hours prior to blood sampling.

1. PK blood samples: 5 ml of blood will be drawn at 30 prior to LSALT peptide infusion for baseline PK measurements. LSALT peptide infusion will begin and run over 2 hours. 5 ml of blood will be drawn at 15, 30, 45 60, 75, 90, 105, 120, 125, 130, 135, 140 (+/- 2 min) minutes, 3 hours (+/- 5 min) from the onset of the LSALT infusion
2. PK blood sample: 24 hours (+/- 30 mins) from the onset of the 1st infusion.
3. PK blood samples: 5 ml of blood will be drawn at 30 prior to LSALT peptide infusion. LSALT peptide infusion will begin and run over 2 hours. 5 ml of blood will be drawn at 15, 30, 45 60, 75, 90, 105, 120, 125, 130, 135, 140 (+/- 2 min) minutes and 3 hours (+/- 5 min) from the onset of the LSALT infusion
4. PK blood sample: 72 hours (+/- 30 mins) from the onset of the first LSALT infusion
5. PK blood sample: 96 hours (+/- 30 mins) from the end of the third LSALT infusion
6. Vital signs dosing day (seated): pre dose (+/-30 mins), 1 hour (+/- 10mins) , 2 hour (+/- 10 mins) 6 hours (+/- 15min) and 10 hours post completion of infusion (+/- 30 mins)
7. 12 lead electrocardiogram (supine): pre dose (+/- 30 mins), 2 hours (+/- 15 mins) and 8 hours post completion of infusion (+/- 30 mins)
8. Pregnancy test will be via serum B-hCG at Screening and a urine pregnancy test at pre dose (Study Day -1,) and follow up

7.3 Investigational Drug Product, Monitoring and Safety Procedures

7.3.1 Investigational Drug Product. The investigational drug product (LSALT peptide) will be supplied to the study site in aqueous solution at -20°C as a single concentration (1 mg/ml) in a glass vial with restricted access to the site pharmacist or designate. All four doses will be derived from the same formulation prior to patient administration. LSALT peptide vials will be single use only. Drug receipt/administration logs and temperature logs will be maintained by the study site using the Drug Accountability Form. The pharmacist/designate will ensure that the total number of vials in the drug dispatch log is present in the shipment from the sponsor. The pharmacist/designate will also ensure that there is no evidence of breakage of the drug vials. The CRO or sponsor must be notified immediately if any discrepancy is identified in the drug or temperature log or if any breakage occurs.

The LSALT peptide vial will be labeled in English and according to local regulatory requirements. The pharmacist or designate will be unblinded.

7.3.2 Drug Administration. LSALT peptide or an equivalent volume of 0.9% sodium chloride will be diluted in 0.9% sodium chloride solution to a volume of 100 ml mini-IV bag by an unblinded pharmacist or designate. The drug will be infused into the patient through a peripheral 18, 20 or 22 g intravenous catheter over 2 hours and under the supervision of the study investigator.

7.3.3 Pharmacy records. The principal investigator or a designate will be responsible for ensuring that the study site maintains an accurate record of the LSALT peptide inventory using the Drug Accountability Form. A coded label will be affixed to the patient CRF to identify placebo and LSALT peptide treated subjects.

7.3.4 Pretreatment Evaluation. 28 days prior to study initiation, enrolled participants will have a complete history and physical examination including vital signs, baseline fasting

laboratory studies (CBC, clinical chemistry), urinalysis, 12-lead electrocardiogram and chest x-ray (single PA view).

7.3.5 Safety Assessment. Patients will be monitored during drug administration and up to 3 weeks thereafter. Patients will be monitored for adverse effects using vital signs (seated, respiratory rate, heart rate, blood pressure, temperature and pulse oximetry), hematology, clinical chemistry, seated, supine single 12-lead electrocardiograms, chest radiography, and urine testing. Adverse events during the study will be reported and graded as per the CTCAE version 5.0.

7.3.6 Laboratory Testing. 25 mL of blood will be drawn for fasting laboratory assessment (hematology and clinical chemistries) at screening, baseline (pre-dose Day 1), and on study days 2, 4, and 7 (refer to Flow Chart). Additional bloodwork will be drawn at day 14 in the MAD cohort. In addition, 5 mL of blood will be collected for pharmacokinetic analysis at 30-minutes pre-dose, then 15, 30, 45 60, 75, 90, 105, 120, 125, 130, 135, 140 minutes, and 3 hours from the onset of the LSALT infusion, 24 hours post drug administration on day 2 (from onset of 1st LSALT dose, SAD and MAD cohort), 72 hours post drug administration on day 4 (from onset of 1st LSALT dose, SAD and MAD cohort), and 96 hours post drug administration on day 7 (from onset of 3rd LSALT dose, MAD cohort). Participants will be required to have fasted from all food and drink except water for at least 8 hours prior to blood sampling.

Baseline hematology will include hemoglobin, hematocrit, total white blood cell count, white blood cell differentiation and platelet count. INR and PTT will also be performed. Clinical chemistry (fasting state) will include total protein, albumin, sodium, potassium, chloride, bicarbonate, random glucose, insulin, calcium, magnesium, phosphate, urea, uric acid, AST, ALT, ALP, LDH, TBili, GGT, creatinine, triglycerides, total cholesterol, and urinalysis (dipstick for protein, blood, glucose, ketones, pH, leukocytes and microscopic examination only if dipstick is not completely negative). Urinalysis will be conducted at the same times as the blood draws for hematology and clinical chemistries.

7.3.7 Women of Childbearing Potential. Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding,) are required to have a negative serum pregnancy test (β-HCG) during screening and at the end of the study treatment.

Female and male participants (along with their female partners) are required to use a method of acceptable contraception, including one barrier method (condom) and one additional highly effective method (i.e., hormonal contraceptive, intra-uterine device) or abstinence for the duration of the study for 90 days following the last dose of study drug.

7.3.8 Duration of Follow-up. Participants are evaluated for adverse events for 72 hours and 6 days after receiving the low dose and single dose of study drug respectively. Patients receiving multiple daily dosing are evaluated for 17 days after receiving the last dose of the LSALT peptide. Participants with adverse events will be followed until resolution or stabilization of the adverse event. Follow-up after the conclusion of the study participation will be per routine clinical care.

8.0 DOSE ESCALATION AND STOPPING RULES

The first 4 participants will each receive a single low ascending dose of the LSALT peptide. Escalation of the dose in the next participant will occur at 72 hours if the prior participant experienced no adverse effects. The SRC will convene 24 hours after dosing of the last participant to determine if any changes in protocol design or SAD dosing are required. 96 hours following completion of this first low dose escalation phase, in the absence of adverse effects, participants in cohorts of 8 will be randomized 3:1 to receive the LSALT peptide or placebo. The dose for the first SAD cohort will be one intravenous infusion of 1.0 mg of LSALT peptide. The first 2 patients in each SAD cohort will be sentinels (1 treatment and 1 placebo). The SRC will convene 24 hours after dosing of the last sentinel patient to determine if any changes in protocol design or dosing are required. Sequential single dosing of LSALT peptide will occur as planned if sentinel participants show no clinical, biochemical or hematologic abnormalities. The SRC will convene 72 hours after dosing of the last participant to determine continuation of the single dose arm and next ascending dose cohort.

7 days following the completion of the SAD study arm, the SRC will convene to determine transition to the MAD study arm, the starting LSALT peptide dose and frequency. Entry into the multiple ascending dose arm will occur if no clinical, biochemical or hematologic abnormalities are observed at the SAD cohorts after 7 days. The starting dose of the MAD will consist of the 3 highest doses that caused no adverse effects in the SAD cohorts.

One adverse event (grade 3 or greater) in a participant or 2 moderate adverse events (grade 2) in the same cohort will result in a study pause and re-evaluation of the protocol. Termination of the trial will occur if 2 or more grade 3 or greater adverse events occur in the same cohort.

9.0 REGULATORY AND REPORTING REQUIREMENTS

9.1 Adverse Events (AEs)

Definition: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

9.2 Severity (Intensity)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website. Severity of AEs will be assessed as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
Grade 3 Severe; Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4 Life-threatening consequences; urgent intervention indicated.

9.3 Assessment of Causality

All AEs (both serious and nonserious) will be assessed for relationship to investigational product by the Investigator. The investigator will assess the relationship of AEs to investigational product administration using the following categories:

Unrelated: The AE is clearly not related to the LSALT peptide and is clearly related to an underlying disease, environmental or toxic factor(s), or other drug/therapy.
Unlikely related: The AE does not follow a reasonable temporal sequence after LSALT peptide administration (eg, too soon or too long after investigational product or investigational product was not taken) and is plausibly related to an underlying disease, environmental or toxic factor(s), or other drug/therapy. For purposes of regulatory reporting, AEs classified as unlikely related will be considered unrelated to the LSALT peptide.
Possibly related: The AE follows a reasonable temporal sequence after investigational product administration but may be related to an underlying disease, environmental or toxic factor(s), or other drug/therapy. There is a reasonable possibility of a causal relationship between investigational product administration and the AE. For purposes of regulatory reporting, AEs classified as possibly related will be considered related to investigational product.
Probably related: The AE follows a reasonable temporal sequence after LSALT peptide administration and is unlikely to be related to an underlying disease, environmental or toxic factor(s), or other drug/therapy. The AE is consistent with the known response pattern of the LSALT peptide and may respond to stopping the LSALT peptide. For purposes of regulatory reporting, AEs classified as probably related will be considered related to the LSALT peptide.
Related: The adverse event is clearly related to the LSALT peptide; a re-challenge confirms the association (not required or desirable in some circumstances but provides strong evidence when it happens).

9.4 Expectedness

An unexpected adverse drug experience is defined as any adverse effect related to the investigational drug product, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

9.5 Serious Adverse Events (SAEs)

Each AE must be assessed and recorded in the eCRF as serious or not serious. Serious AEs must be reported as described in Section 7.9. International Conference on Harmonization Guidelines and the Code of Federal Regulations (CFR; 21 CFR 312.32, revised as of 01 April 2017). An SAE is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- *A life-threatening adverse event;
- Inpatient hospitalization for at least 24 hours or prolongation of existing hospitalization;

- A persistent or significant disability/incapacity (i.e. substantial disruption of the ability to conduct normal life functions); or

- A congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

*A life-threatening adverse event is defined as any adverse drug experience that places the participant (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.6 Pregnancy

Should a female participant become pregnant or suspect she is pregnant while participating in this study, or should a male patient's partner become pregnant or suspect she is pregnant while the male is participating in this study, the treating investigator should be informed immediately. Female patients will be withdrawn from the study, and all pregnancies will be reported along the same timelines as a SAE. The Human Research Ethics Committee (HREC) and the sponsor will be informed. The participant will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage and congenital abnormalities will be reported as SAEs. The follow-up period will be deemed to have ended when the health status of the child has been determined on its birth and followed up for 8 weeks following the birth for any potential abnormalities.

9.7 Reporting of Serious Adverse Effects

The Study Site PI, or delegate is required to promptly notify the Sponsor of the following events:

- Any unanticipated problems including serious adverse events involving risks to participants or others which occur at the study site, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the Sponsor.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

Any SAE must be reported by the investigator if it occurs during the clinical study or within 1 day of receiving the LSALT peptide, whether or not the SAE is considered to be related to the LSALT peptide. An SAE report consists of the SAE report form, and where applicable the concomitant medication/history form. A copy of these forms must be emailed or faxed within 24 hours for the attention of the Sponsor's safety representative:

Attention Syneos Health Safety & Pharmacovigilance
Email: safetyreporting@syneoshealth.com (preferred)
Local Toll-Free Fax (Australia): 1 800 256 952
Alternate (Global) Fax: +1 877 464 7787

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained and provided upon request.

9.8 Protocol Exceptions

A planned deviation from the approved protocol that are under the research team's control must be approved by the sponsor and ethics committee. Waivers are not acceptable.

9.9 Unblinding

Adverse events Grade 2 or greater will trigger unblinding to allow study personnel and the PI to best manage the study participant and clinical situation.

10.0 PHARMACEUTICAL INFORMATION

10.1 LSALT Peptide

10.1.1 LSALT Peptide Description.

LSALT is an unmodified peptide with the molecular formula: Leu-Ser-Ala-Leu-Thr-Pro-Ser-Pro-Ser-Trp-Leu-Lys-Tyr-Lys-Ala-Leu

Molecular weight: 1775 Da

10.1.2 Mechanism of Action

LSALT peptide is a non-enzymatic inhibitor of dipeptidase-1

10.1.3 Manufacturer

CS Bio Co.
20 Kelly Court
Menlo Park, CA
94025 USA

10.1.4 Dosage

Supplied as 1 mg/ml solution in 5 ml 0.9% sodium chloride. Dosages for this study are 0.01 mg, 0.1 mg, 0.3 mg, 0.5 mg, 1.0 mg, 2.5 mg and 5 mg.

10.1.5 Storage

LSALT peptide in 0.9% sodium chloride is stored at -20° C and thawed immediately before use as per pharmacy manual.

10.1.6 Administration

LSALT peptide is diluted in 100 ml of 0.9% sodium chloride and administered intravenously over 2 hours ± 5 minutes. Based upon evaluation of tolerability and safety of the first cohort, and consistent with the adaptive design, infusion rates could be increased or decreased for subsequent cohorts, as determined by the SRC.

11.0 MONITORING AND QUALITY

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an informed consent form (ICF) and is administered study drug. In accordance with cGCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable. The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authority's direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

12.0 AUDIT AND INSPECTION

Study sites and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

13.0 ETHICS, REGULATORY, INFORMED CONSENT AND PATIENT CONFIDENTIALITY

13.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center the protocol, the ICF, other written material given to the participants, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the participants or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

13.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating country, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

13.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

13.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no participant undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the participant of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The participant should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the participant will be given ample time to consider the study. Participants will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the participant or their authorized representative.

It should be emphasized that the participant may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the participant is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study participants will be informed about this new information and reconsent will be obtained.

13.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the Australian Therapeutic Goods Administration (TGA), as well as that of any other applicable agency(ies), will be granted direct access to the study participants' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the participants to the extent permitted by the law

and regulations. In any presentations of the results of this study or in publications, the participants' identity will remain confidential.

14.0 DATA AND SAFETY MONITORING

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the Sponsor.

15.0 PHARMACOKINETIC STUDIES

Blood samples will be drawn from participants for pharmacokinetic analysis at 15- and 30-minutes pre-dose and then 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post drug administration on day 1 (SAD and MAD cohort) and day 3 (MAD cohort).

Pharmacokinetic analysis will be performed using validated analytic method.

16.0 STATISTICAL ANALYSIS

Demographics and baseline characteristics will be tabulated and summarized by SAD/MAD dose level. Physical examination and medical/surgical history data will be listed by participant.

All clinical safety and tolerability data will be listed for each participant and summarized by dose. Vital signs and ECG parameters will be tabulated and summarized by SAD/MAD dose level. Laboratory values will be listed, along with comments as to clinical significance for values outside the laboratory's normal ranges.

Treatment-emergent adverse events, following the investigational product dosing, will be listed and summarized by dose level. All adverse events reported in this study will be coded using MedDRA.

Individual plasma concentrations and blood collection times will be listed by participant. Summaries of concentration data will include mean, standard deviation and coefficient of variation by SAD/MAD dose level at each scheduled collection time. Summaries of PK parameters by SAD/MAD dose level will include mean, SD and CV.

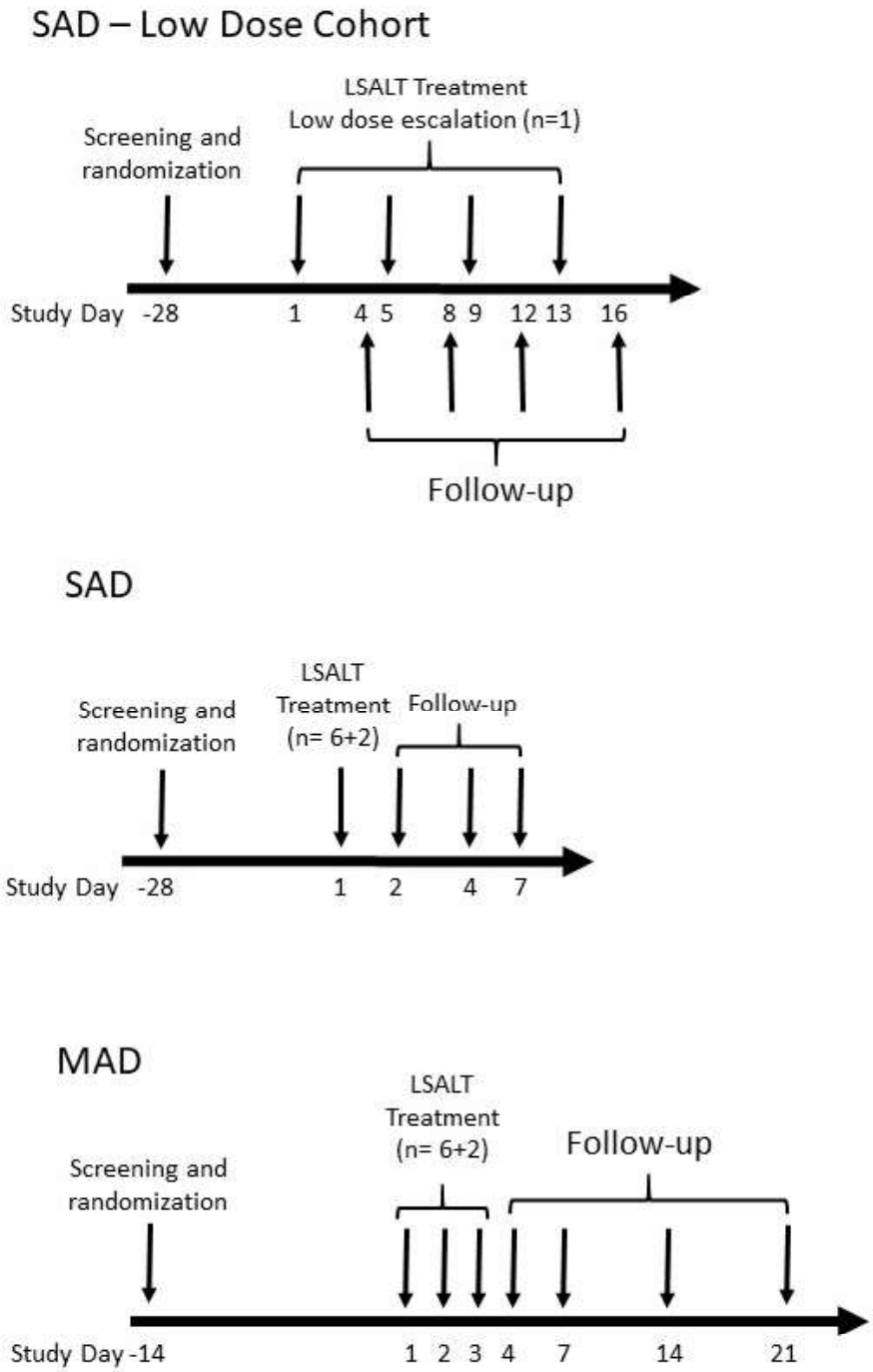
17.0 RECORD RETENTION

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last participant), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all participant

medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study.

18.0 SCHEMA


SAD – Low Dose Cohort
LSALT Treatment
Low dose escalation (n=1)
Screening and randomization
Study Day -28
1
4 5
8 9
12 13
16
Follow-up
SAD
LSALT Treatment (n= 6+2)
Follow-up
Screening and randomization
Study Day -28
1
2
4
7
MAD
LSALT Treatment (n= 6+2)
Follow-up
Screening and randomization
Study Day -14
1 2 3 4
7
14
21

19.0 REFERENCES

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