PHASE I, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF SNS-301 IN CANCER PATIENTS

Study product: SNS-301

Protocol number: SNS0216

IND: 16963

Phase: 1

Version: 5.0

Amendment Date: 12 June 2018

Study Sponsor:

Sensei Biotherapeutics, Inc.

620 Professional Drive

Gaithersburg, MD 20879

Regulatory Statement

This study will be performed in compliance with the protocol and in accordance with Good Clinical Practice (International Conference on Harmonization, Guidance E6, 1996), principles of human subject protection, and applicable country-specific regulatory requirements.

Confidentiality Statement

This Study Protocol is produced on a word-processing system and bears no signatures. The approval of the Study Protocol is documented in a separate Approval Document.

SPONSORS PROTOCOL SIGNATURE PAGE

Sponsor:	Sensei Biotherapeutics, Inc.
Protocol Title	**Phase I, Open-Label Trial To Evaluate The Safety And Immunogenicity Of SNS-301[1] In Cancer Patients**
Protocol Number	SNS0216
Protocol Version	Version 5.0
Amendment Date:	12 June 2018

I approved the protocol and confirm that the protocol follows the current ICH/GCP guidelines.

_____

Steve Fuller, Ph.D. Date

Chief Operating Officer

Sensei Biotherapeutics, Inc.

[1] Due to the company changing their name from Panacea Pharmaceuticals to Sensei Biotherapeutics, the drug PAN-301-1 was renamed SNS-301.

TABLE OF CONTENTS

1. SYNOPSIS

Protocol number:	SNS0216
Protocol title:	Phase I, Open-Label Trial to Evaluate the Safety and Immunogenicity of SNS-301 in Cancer Patients
Phase of development:	Phase I
Objectives (Part 1):	Primary To determine the maximum tolerated dose (MTD) of SNS-301, based on the incidence of dose limiting toxicities (DLT) and the maximum administered dose of SNS-301, when administered every 21 days in patients with biochemically relapsed prostate cancer. Secondary To assess the overall safety of SNS-301.
Study design:	This is a Phase I, open-label, study of SNS-301, an HAAH-directed nanoparticle vaccine, given intradermally in cohorts of patients with biochemically relapsed prostate cancer, using a fixed dose-escalation schema every 21 days to establish the MTD. Following informed consent and screening, archived prostate tumor tissue (if available), and patient fresh serum will be tested for the expression of HAAH. Patients who test positive for HAAH expression in either archived tumor tissue (if available), or fresh serum may be continued in the study. Baseline biochemical testing (chemistry, complete blood count [CBC], coagulation panel, CH-50, and prostate-specific antigen [PSA],) will be obtained prior to study treatment. Patients who are negative for HAAH in archived tumor tissue or fresh serum can be followed for PSA levels over the next 6 months, and, if levels increase appreciably, they can be retested for HAAH. If HAAH is positive at any time within the 6-month period, the patient can be enrolled. Treatment will consist of single repeated doses of SNS-301 administered every 21 days for 3 doses. A traditional 3+3 dose-escalation schema will be used to determine the MTD of SNS-301for the first 2 doses and a modified dose-escalation schema for the remaining dose. Planned doses of SNS-301 are 2.0×10^{10}, 1.0×10^{11} and 3.0×10^{11} particles per administration diluted to 1 mL and administered intradermally. Additional patients will be enrolled at the highest dose level until at least 6 patients can be evaluated even if no DLTs are observed at the dose. Planned treatment may continue for two additional doses of SNS-301 administered every 21 days. Serum and whole blood samples will be obtained on the day of study treatment, at Day 1, Day 8, Day 15, and Day 22 during the first cycle. For patients who continue to receive study treatment, biochemical and immunologic testing will continue every 21 days. The MTD will be determined over the first 21-day interval following a single dose of SNS-301 in 3 dose cohorts. The MTD will be considered the dose level lower than the dose producing ≥2 DLTs in 3-6 patients. Patients who withdraw in cycle 1 for reasons other than safety or toxicity will be replaced. Any of the following, if judged to be associated with SNS-301

	(i.e., possibly-, probably-, or definitely related to), will be considered a DLT using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03: 1) Grade 4 non-hematological toxicities (excluding alopecia) of any duration 2) Grade 3 non-hematologic (non-laboratory) toxicity lasting > 3 days despite optimal supportive care 3) Any Grade 3 or Grade 4 non-hematologic laboratory value if: a). Medical intervention is required to treat the patient; b), the abnormality leads to hospitalization; c). The abnormality persists for >1 week. 4) Grade 4 hematologic toxicity, other than those specified in criteria 5 and 6 below, lasting > 7 days 5) Grade 3 or Grade 4 febrile neutropenia of any duration 6) Grade 3 thrombocytopenia in combination with a grade 3 or greater blood and lymphatic system disorder 7) Grade 3 AST or ALT that is associated with a grade 2 rise in bilirubin The recommended Phase 2 dose (RP2D) will be defined as the highest dose administered if no MTD is observed. Dose cohorts will be enrolled sequentially and no dose escalation will occur until all patients in the current cohort complete the first 21-day cycle. After the first patient in each cohort has demonstrated adequate safety and tolerability for at least 21 days, the next 2 patients in the cohort may be enrolled. When at least 3 patients have reached Day 21 if none of the first 3 patients experiences a DLT, then dose-escalation to the next level can begin. Multiple patients can be in the screening phase but the first eligible patient able to be treated is assigned the treatment slot that is available for study. A safety assessment of administration site reactions (ASR) will be made by the Investigator at least 30 minutes (or later) following each dose of study drug using the (NCI-CTCAE V4.03). Enrollment will be held if an ASR of grade 3 or greater (NCI-CTCAE V4.03) is observed, until the event resolves. In the event enrollment is held for an ASR, the Sponsor and Investigator will evaluate the outcome of the ASR and must agree to continued enrollment. In patients who tolerate SNS-301, additional treatment may be continued with single doses of SNS-301 at their current dose level, to maintain geometric mean titer (GMT) of HAAH antibodies to no less than 4 times the baseline value for at least six months (9 injections). Treatment will be terminated with the 9th injection or will otherwise be terminated at any time upon the observance of PSA doubling < 90 days or occurrence of unacceptable toxicity. After termination, patients will be followed for an additional 6 months with monthly PSA levels and imaging studies as needed. If an unacceptable rise is detected in the patient's PSA levels following treatment discontinuation, patients shall be eligible for immediate resumption of therapy.

	Once the MTD/RP2D is determined, patients receiving ongoing treatment may be escalated to that dose for subsequent treatments. These patients will continue to be followed for safety and biochemical PSA monitoring. **Pharmacodynamics:** Exploratory pharmacodynamic (PD) analysis will be performed using dose, vaccine-specific antibody response (geometric mean of titer), antigen-specific T and B cell indices, and the relative expression of HAAH in each patient's tumor. The PD will be balanced and optimized to the degree of antigen-specific immune response and minimized for the production of regulatory immune processes. **Other Safety:** Safety will be evaluated by the incidence and severity of ASRs, changes in biochemical safety measures, general incidence and types of AEs, serious adverse events (SAEs), and other overt toxicities.
Number of patients/ centers:	This is a multi-center dose-escalation study with an extension study at the RP2D. Up to approximately 18 patients will be studied.
Randomization procedure:	The study is an open-label, dose-escalating, non-randomized Phase 1 clinical study with a dose extension phase. No randomization will be performed.
Inclusion criteria:	1. Signed and dated written Ethics Committee approved informed consent 2. Men aged 21 to 85 years with a histologic diagnosis of prostate cancer with a biochemical relapse following definitive local therapy (RP or radiation therapy) 3. Patients are not eligible or are unwilling to receive additional definitive therapy following relapse (either RP or radiation therapy) 4. No prior cytotoxic chemotherapy for the current cancer 5. Normal electrocardiogram (ECG) or ECG with no clinically significant findings as determined by the Principal Investigator 6. Presence of biochemically relapsed prostate cancer defined as either: 1) PSA > 2 ng/mL 1 year following initial definitive treatment for prostate cancer: or, 2) PSA doubling time (greater than 0.2 ng/mL) < 12 months; or, 3) PSA velocity > 2 ng/mL/year at any time following radical prostatectomy or radiation therapy. 7. Positive expression of HAAH in either archived tumor tissue (if available) or fresh serum 8. No clinical or radiologic evidence of distant metastatic disease as measured by pelvic MRI or CT scan in addition to bone scan. These studies will need to be performed within 56$\pm$7 days prior to the start of the study. 9. No history of immunosuppressive disease. Active autoimmune disease is defined as any disease process that has specifically needed administration of immune suppressive and or cytoreductive therapy currently or within the last 1 year. 10. No evidence of active autoimmune disease 11. Able and willing to comply with all study procedures

Exclusion criteria:	1. PSA doubling time of < 3 months 2. Participation in a clinical trial within 30 days of prior to enrollment 3. Prior major surgery or radiation therapy within 4 weeks of enrollment 4. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or the evaluation of any study endpoint 5. Screening blood counts of the following: Hematopoietic: Absolute neutrophil count $\leq$ 1500/μL, Platelets $\leq$ 100,000/μL, Hemoglobin $\leq$ 9 g/dL; Liver/Metabolic: Alanine aminotransferase (ALT) and aspartate transaminase (AST) $\geq$ 2.5 × ULN range, Total bilirubin $\geq$ 2 × ULN, Albumin $\leq$ 2.8 g/dL; Renal: Creatinine clearance $\leq$ 50 mL/min as predicted by the Cockcroft-Gault formula 6. Subjects whose partners are women of child-bearing potential (WOCBP) must use an adequate method of birth control while on study drug and at least for 3 weeks after discontinuation of study drug 7. Current or anticipated concomitant immunosuppressive therapy (excluding non-systemic inhaled, topical skin and/or eye drop-containing corticosteroids) 8. Any concurrent condition requiring the continued use of systemic steroids (see above) or the use of immunosuppressive agents including methotrexate. All other systemic corticosteroids must be discontinued at least 4 weeks prior to first study treatment 9. Receipt of any blood product within 1 month of enrollment 10. Receipt of any vaccine within 4 weeks of enrollment 11. Active drug or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements 12. Been imprisoned or compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness 13. Patients who have a history of coagulopathies, thrombosis or who are receiving active anticoagulation for any condition, such as but not limited to, artificial heart valves, atrial fibrillation, etc. 14. Any other conditions judged by the Investigator that would limit the evaluation of a subject
Study Product Formulation	SNS-301 consists of lambda bacteriophages expressing HAAH-1λ on the head of the bacteriophage. The bacteriophages are prepared in a liquid formulation in phosphate-buffered saline, pH 7.4. A 1mL dose filled in a 3M® glass cartridge with a butyl rubber stopper and crimp cap seal.

Route of administration:	Intradermally: vaccine to be delivered by a single-use 3M® hollow micro structured transdermal system (hMTS) device.
Dose regimen:	Escalating doses of 2.0 x 10^{10} and 1.0 x 10^{11} particles will be administered to cohorts of 3 patients and 3.0 x 10^{11} particles will be administered to a cohort of 6 patients every 21 days to assess the MTD. The RP2D will be considered the MTD unless convincing safety, PD, or PK data suggest otherwise. At such a point, these data will be shared with the FDA and the RP2D will be changed or additional dose escalation cohorts will be proposed If needed. Additional patients will be enrolled at the highest dose level until at least 6 patients can be evaluated even if no DLTs are observed at the dose. Patients in the dose-escalation phase may continue to receive single doses of SNS-301 at their original dose level every 21 days or until the PSA doubling is < 90 days or unacceptable toxicity as determined by the Principal Investigator is observed (either for that patient or in their dose cohort). Once the MTD/RP2D is determined, patients receiving ongoing treatment may be escalated to that dose for subsequent treatments and receive a maximum of 9 injections. Patients who have received more than 9 injections due to the timing of the amendment limiting therapy to 6 months (9 doses), will be stopped at their last dose received and be followed for 6 months as with other patients. These subjects will continue to be followed for safety and biochemical PSA monitoring on a monthly basis for 6 months and are eligible to resume SNS-301 in case of increases in PSA doubling to < 90 days or other evidence of disease progression and decline in immunological parameters.
Study Endpoints:	<u>Primary endpoint:</u> • To determine the MTD • Determine the RP2D if different than the MTD • Determine the DLTs associated with SNS-301 <u>Secondary endpoints:</u> • Incidence of administration site reactions • Biochemical safety and tolerability • Geometric mean titers of anti-HAAH antibodies by dose • Antigen-specific CTL responses by dose • Production of B cell and T cell response of interest <u>Clinical secondary endpoints:</u> • Change in the PSA velocity • Reduction in the PSA doubling time from pre-baseline <u>Pharmacodynamic secondary endpoints:</u> • Duration of antigen-specific anti-HAAH antibody titers • Changes in the amplitude or duration of the production of anti-HAAH antibodies • Correlation of anti-HAAH titers and serum HAAH levels
Study evaluations:	Following informed consent signature, archived prostate tumor tissue, and patient serum will be tested for the expression of HAAH. Only patients who test positive for HAAH expression in archived tumor tissue (if available) or fresh serum may be continued in the study. The following evaluations will be performed: • Medical/oncology history, demographics: Screening

	• Signs and symptoms (baseline): Screening, Day 1 • Physical examination: Screening and end of study (EOS) • Symptom-directed physical examination: Day 1, Day 8, Day 15, Day 22, Day 43 and if additional treatment is given, at 21-day intervals thereafter • Biochemical testing (chemistry, CBC, coagulation, CH50): Screening, Day 1, Day 22, Day 43 and if additional treatment is given at 21-day intervals thereafter and EOS • Biochemical testing (chemistry, CBC, coagulation, CH50) Day 8 and Day 15 during cycle 1 • Study treatment administration: Day 1, Day 22, Day 43 and if additional treatment is given, at 21-day intervals thereafter for a total of 9 injections. Patients who have received more than 9 injections due to the timing of the amendment that details limiting therapy to 6 months (9 doses), will be stopped at their last dose received and be followed for 6 months as with other patients. Patients with off-treatment evidence of progression and declining HAAH immune parameters during the 6-month observation period will have the option of immediately resuming therapy on study protocol. • Physician administration site assessment: Day 1, Day 8, Day 22, Day 43 and if additional treatment is given at 21-day intervals thereafter; and EOS • Safety evaluation of subject to permit continued enrollment in each cohort Day 21for every first and last patient in a dose level • Eastern Cooperative Oncology Group (ECOG) performance score: Screening, Day 1, Day 8, Day 15, Day 22, Day 43 and if additional treatment is given, at 21-day intervals thereafter; and EOS • Prostate-specific antigen (PSA) assessment: Screening, Day 1, Day 22, Day 43 and if additional treatment is given, at 21 day intervals thereafter; until injection number 9 (or last dose otherwise) and EOS. Afterwards PSA levels will be obtained on a monthly basis for a total of 6 months. • Immunologic blood collection: Screening, Day 1, Day 22, Day 43 and if additional treatment is given, at 21 day intervals thereafter; until injection number 9 (or last dose otherwise) and EOS. Afterwards levels will be obtained on a monthly basis for a total of 6 months. • Adverse events and concomitant medications (after the patient receives study drug): Screening, Day 1, Day 8, Day 15, Day 22, Day 43 and if additional treatment is given, at 21 day intervals thereafter; until injection number 9 (or last dose otherwise) and EOS. Afterwards history will be obtained on a monthly basis for a total of 6 months. • Vital signs, ECG: Screening, Day 1, Day 22, Day 43 and if additional treatment is given, at 21 day intervals thereafter; until injection number 9 (or last dose otherwise) and EOS. Afterwards data will be obtained on a monthly basis for a total of 6 months.
Statistical analysis:	No formal statistical analysis will be performed, however, statistical derivation of all data will be derived by dose cohort and displayed for inspection.

	For the dose-escalation phase of the study, cohorts of 3 or 6 patients will be screened, registered and treated at each dose level. The actual sample size may vary depending on the incidence of DLT during Cycle 1 at a given dose level. Once the MTD/RP2D is determined, additional patients may be accrued to provide for 6 patients in the MTD cohort. Approximately, 18 patients will be screened, registered and treated in the trial. The primary safety analysis will assess MTD and AEs, clinical laboratory tests, and tolerability, based on the combined evaluation of immunogenicity and incidence of DLTs in each patient.
Study duration:	The duration of the study for each patient will include an up to 8-week screening phase, 21-day study treatment cycles for 9 cycles and 6 months of follow up including monthly PSAs and an end of study visit (28 days post last dose of study treatment). Patients may continue to receive single repeated doses of SNS-301 at their original dose level (or at the MTD when it is determined) every 21 days for a total of 9 doses or until the observance of PSA doubling < 90 days or unacceptable toxicity (either for that patient or in their dose cohort). Patients who have received more than 9 injections due to the timing of the amendment limiting therapy to 6 months (9 doses), will be stopped at their last dose received and be followed for 6 months as with other patients. Patients with evidence of progression and declining HAAH immune parameters during this 6-month follow up period will have the option of immediately resuming therapy on study protocol.

1.1 TIME AND EVENTS SCHEDULES

Table 1: Time and Events Schedule

Assessment	Screen (D-56+7[e] to D0)	Cycle 1 Assessments			Cycle 2-3		Additional Treatments	Follow-up/End of study
		D1	D8 ± 2	D15± 2	D22 ± 3	D43 ± 3	Every 21 ± 3 day	Every 28 ± 3 days after final treatment for 6 Months
Signed Informed Consent	X							
HAAH assessment[a]	X							
Demographics	X							
Medical/Oncology History	X							
Tumor Burden Evaluation[d]	X							
Baseline Signs and Symptoms	X							
Physical Examination	X							X
Symptom-Directed Physical Examination		X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X
ECOG Performance Score	X	X	X	X	X	X	X	X
ECG	X	X			X	X	X	X
PSA	X	X			X	X	X	X
Hematology[b]	X	X	X	X	X	X	X	
Chemistry[b]	X	X	X	X	X	X	X	
Coagulation, CH50[b]	X	X	X	X	X	X	X	
Study Treatment administration		X			X	X	X	
Physician Administration Site Assessment		X	X		X	X	X	
Immunologic Blood Collection[c]		X			X	X	X	X
Cohort enrollment evaluation					X			
Concomitant Medications Collection		X	X	X	X	X	X	X
Adverse Events Assessments[f]		X	X	X	X	X	X	X

Abbreviations: ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen

a HAAH assessment: following informed consent, archived prostate tumor tissue and patient serum will be tested for the expression of HAAH. Only patients who test positive for HAAH expression in archived tumor tissue (if available) or fresh serum may be continued in the study. HAAH assessments are not subject to the 56-day screening window and are valid for 6 months. Patients who are negative for HAAH may be followed for 6 months and if PSA rises over that period time, they can enroll in the study provided that tissue or fresh serum is positive for HAAH

b Biochemical testing (chemistry, complete blood count, coagulation, and total complement CH50,) to be obtained within 14 days prior to study drug administration if screening period is between 3 and 8 weeks. PSA levels are also to be evaluated at screening and within 14 days prior to study drug administration if screening period is between 3 and 8 weeks.

c Immunologic blood collection: to be taken pre-dose on the day of study drug administration (Day 1) and every 21 days thereafter. Following the 9th dose (or last dose otherwise), PSA levels and other assessments will be followed on a monthly basis for 6 months. Patients with evidence of progression and declining HAAH immune parameters will have the option of resuming therapy on the study protocol.

d Baseline radiological tumor burden evaluation consists of a baseline pelvic MRI or CT scan in addition to bone scan. These studies will need to be performed within 56 days (+ 7 days) prior to the start of the study.
e Patients that have a delay in screening beyond 56-days may be re-screened for randomization.
f Adverse events that occur post patient receiving study drug. Should Adverse event occur prior to patient receiving study drug they will be captured as Medical History.

2. TERMS, ACRONYMS, ABBREVIATIONS

Term	*Definition*
7-ADD	7-amino actinomycin D
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
APC	Antigen-presenting cells
ASR	Administration site reaction
AST	Aspartate aminotransferase
°C	Celsius
CBC	Complete blood count
CFR	Code of Federal Regulations
CFSE	Carboxyfluorescein succinimidyl ester
CH-50	Total complement activity
CpG	5'-c-phosphate-G-3'(a DNA sequence)
CTL	Cytotoxic CD8+ T-lymphocytes
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
FDA	Food and Drug Administration (U.S.)
GMT	Geometric mean titer
gpD	Head DNA stabilization protein of Bacteriophase lambda
HAAH	Human aspartyl-asparaginyl-β-hydroxylase
hMTS	3M® hollow microstructured transdermal system
ICF	Informed consent form
IgG	Immunoglobulin G
IND	Investigational New Drug
IRB	Institutional review board
irRC	Immune-related response criteria
kDa	Kilodalton
LVEF	Left ventricular ejection fraction

Term	*Definition*
MACS	Magnetic activated cell sorting
MHC	Major histocompatibility complex
mL	Milliliters
M0	Non-metastatic cancer
M1	Metastatic cancer
MTD	Maximum tolerable dose
NCI-CTCAE V4.03	National Cancer Institute Common Terminology Criteria for Adverse Events V 4.03
PBMC	Peripheral blood monocytes
SNS-301	HAAH bacteriophage lambda constructs: HAAH-1λ
PSA	Prostate-specific antigen
RP	Radical prostatectomy
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
WOCBP	Women of child-bearing potential

3. INTRODUCTION

3.1 Primary Disease and Study Treatment Information

Human aspartyl-asparaginyl-β-hydroxylase (HAAH), also known as aspartate-β-hydroxylase, is an ~86 kDa type 2 transmembrane protein that belongs to the α-ketoglutarate-dependent dioxygenase family [1]. It is a highly conserved enzyme, which catalyzes the hydroxylation of aspartyl and asparaginyl residues in epidermal growth factor-like domains of proteins including Notch and homologs [2]. HAAH was initially identified in a novel screen to identify cell surface proteins up-regulated in liver cancer. It has subsequently been detected in a diverse array of solid and blood cancers, including: liver, bile duct, brain, breast, colon, prostate, ovary, pancreas, and lung cancers as well as leukemia. HAAH is not found in significant quantities in normal tissue or in proliferative disorders.

Over-expression of HAAH has been demonstrated to be sufficient to induce cellular transformation, increase cellular proliferation and cellular motility and suppression of HAAH expression (small interfering ribonucleic acid) or neutralized activity (monoclonal antibodies) returns cancer cells to a normal phenotype. In cancer cells, it has been shown to be translocated to the cellular surface where it is not normally located. Because HAAH is an embryonic antigen, and as such presents self-antigen tolerance, it is relatively difficult to elicit a robust immune response against it. Thus, we posited that effective priming of antigen-presenting cells (APC) by HAAH antigen is an essential step to overcome tolerance. Indeed, *in vitro* activation of dendritic cells with HAAH, prior to re-administration to patients has shown promising results for liver cancer therapy [3]. Unfortunately, this process is cumbersome, expensive, time consuming and impractical for mass scale immunotherapy.

Bacteriophage display is a simple, inexpensive and practical way of achieving favorable presentation of peptides to the immune system. The phage contains deoxyribonucleic acid (DNA) fragments that present the phage CpG motifs, which are known to stimulate the innate immune response and activate the major histocompatibility class (MHC) class II pathway in APC. Previous findings have revealed that recombinant bacteriophage can prime strong CD8+ T-lymphocyte (CTL) responses both in vitro and in vivo against epitopes displayed in multiple copies on their surface [4], activate T-helper cells [5] and elicit the production of specific antibodies [6, 7] all normally without adjuvant. Thus we have selected bacteriophage as a platform for eliciting anti-HAAH immune responses. Bacteriophage are ubiquitous and essentially innocuous to humans, however, as an added safety mechanism, they may be neutralized rendering them non-infective to host bacteria while retaining their immunostimulant properties. Once neutralized, the bacteriophage effectively becomes a nanoparticle, for enhanced delivery of protein fragments to APC.

We have designed a bacteriophage lambda system to display HAAH peptides fused at the C-terminus of the head protein gpD of phage lambda. The phage carry 200-300 copies of the gpD protein on their head and thus display many copies of an approximately 25 kDa molecular weight fragment of HAAH on their surface. The drug substance is one of these HAAH bacteriophage lambda constructs: HAAH-1λ (SNS-301).

3.2 Previous Non-Clinical Experience

Nonclinical studies have focused on the immunogenicity and efficacy of the HAAH Nanoparticle Vaccine in rodent models. Nonclinical toxicology studies have been completed and are described below.

The nonclinical data generated to date include:

- Demonstration of immunogenicity in mice and rats
- Demonstration of dose response to both amount of vaccine and number of doses
- Demonstration of both humoral and cellular immunity
- Demonstration of enhanced immunogenicity for intradermal compared to intramuscular immunization
- Efficacy data in three rodent tumor models, including solid tumors and metastases
    - Inhibition of solid tumor growth and metastases with the mouse hepatocellular carcinoma cell line, BNLT3
    - Inhibition of solid tumor growth, lung metastases and mortality with the mouse breast cancer cell line, 4T1
    - Inhibition of metastases with the rat prostate cancer cell line, MLLB-2

The data listed above have been generated in three laboratories, which provide corroboration of the nonclinical observations in multiple environments and with multiple technical staff. It is important to note that there has been no local reactogenicity or adverse events (AEs) associated with the administration of multiple doses of the HAAH Nanoparticle Vaccine in mice and rats. These vaccines are immunogenic, show efficacy in three tumor model systems and are safe in the doses given to rodents. In total, the data strongly support the potential utility of the HAAH-1λ vaccine for the immunotherapy of cancer.

It is anticipated that the HAAH Nanoparticle Vaccine will also prove to be safe in humans. Bacteriophages are ubiquitous in our environment. All humans are constantly exposed to large numbers of bacteriophage with no apparent harm. The relatively low dose and dose frequency of a vaccine as compared to other cancer drugs, both chemical and biological, also predict that these materials should be quite safe in human subjects.

Panacea has conducted a repeated dose study in rats that assessed the toxicity of the SNS-301 (previously named PAN-301-1) HAAH nanoparticle vaccine when administered intradermally at the same three dose levels (2×10^{10}, 1×10^{11} and 3×10^{11} particles) and same dose schedule (3 doses given at 21 day intervals) as proposed for this human study, followed by 2 week and 4-week recovery periods. These dose levels were chosen based on demonstrated immunogenicity and efficacy in the animal models described above. The conclusions of the study were that treatment with SNS-301 at doses up to 3×10^{11} particles had no effect on mortality, physical examinations, cage-side observations, dermal Draize observations, body weights or body weight changes, food consumption, body temperature, ophthalmologic observations, gross pathology, absolute and relative organ weights, hematology or clinical chemistry. A slightly prolonged but non-adverse PT time in males given $\geq 1 \times 10^{11}$ particles and females given 3×10^{11} particles persisted through the first recovery period (2 weeks post-3rd injection). The prolonged PT time resolved in males by the second recovery period (4 weeks post-3rd injection) but remained minimally prolonged in females given 3×10^{11} particles. Test article-related microscopic findings were present in the injection site in animals given $\geq 1 \times 10^{11}$ particles and consisted of mild or moderate mononuclear or mixed inflammatory cell infiltrates in the dermis and/or subcutis. These findings were considered non-adverse and resolved during recovery. Additionally, the SNS-301 vaccine demonstrated a significant antibody response that was dependent on both the dose level and number of doses administered.

These toxicology results demonstrate safety of the SNS-301 HAAH nanoparticle vaccine and support the planned multiple dose Phase 1 study of the HAAH Nanoparticle Vaccine in humans described in this protocol.

3.3 Current Clinical Experience

Review of Current Clinical Data with SNS-301

Exposure

A total of 12 patients have been treated with at least 5 doses of SNS-301. All 12 of these patients are subjects in the current IND protocol.. Seven patients in the current study have already received 9 or more injections and will continue to receive treatment until the current amendment limiting dosing to 9 doses becomes effective. The listing of patient identifiers, primary cancer data, and exposure data are provided in Table 2.

Table 2: Patients Treated with SNS-301

Patient ID	IND Study (Y/N)	Primary Cancer	Date of First Dose	Dose Administered	Number of Doses
001-001	Yes	Prostate	1/5/17	2.0×10^{10}	11
				1.0×10^{11}	5
				3.0×10^{11}	6
004-001	Yes	Prostate	4/19/17	2.0×10^{10}	7
				1.0×10^{11}	5
				3.0×10^{11}	7
004-002	Yes	Prostate	5/23/17	2.0×10^{10}	5
				1.0×10^{11}	5
				3.0×10^{11}	7
004-004	Yes	Prostate	6/20/17	1.0×10^{11}	9
				3.0×10^{11}	7
004-003	Yes	Prostate	7/18/17	1.0×10^{11}	7
				3.0×10^{11}	2
003-002	Yes	Prostate	7/25/17	1.0×10^{11}	6
				3.0×10^{11}	5
001-003	Yes	Prostate	8/21/17	3.0×10^{11}	12
003-006	Yes	Prostate	11/13/17	3.0×10^{11}	8
004-006	Yes	Prostate	11/20/17	3.0×10^{11}	8
004-007	Yes	Prostate	11/29/17	3.0×10^{11}	8
001-004	Yes	Prostate	12/20/17	3.0×10^{11}	7
003-007	Yes	Prostate	1/29/18	3.0×10^{11}	5

Local Tolerability

Local tolerability of the drug administration is being evaluated after each dose at 1 hour, 7 days and after each new injection. The assessment of injection site reactions includes the evaluation of injection site pain, tenderness, erythema, erythema wheal measurement, swelling, and swelling wheal measurement. A total of 142 doses of SNS-301 have been administered to these 12 patients. In all cases, there have been no reports of a local injection site reaction immediately (1hr) following the first injection, at day 7 post injection, or following the second and subsequent injections.

Biochemical Safety

In the IND study patients, biochemistry, hematology, and PT/PTT/INR are measured pre-dose, at Day 8, Day 15, and Day 22 just prior to the second dose of study drug on an ongoing basis for each cycle of study drug. Patients treated compassionately have blood testing performed per the standard of investigator care. There have been no clinically significant changes in any analyte measured in the IND-treated patients over the course of the study. Further, there have been no reports of any laboratory abnormalities in patients receiving compassionate use SNS-301.

CH50 Complement

Total complement (CH50) has been determined pre-treatment for each new dose, at Day 8, Day 15, and Day 22 prior to the next dose. There were no clinically relevant changes in CH50 acutely (Day 8) or chronically every 22 days following multiple administrations of study drug.

Clinical Safety

There have been no serious adverse events reported in any of the 12 patients exposed to SNS-301. Three patients have experienced a total of 5 adverse events deemed to be possibly related to study drug as outlined in Table 3. All AEs are ≤ Grade 3.

Table 3: Adverse Events

Patient Number	Adverse Event	Date	Dose
001-001	Migratory Arthralgia	9/4/17	1.0×10^{11}
001-001	Migratory Arthralgia	11/20/17	1.0×10^{11}
001-001	Migratory Arthralgia	12/11/17	1.0×10^{11}
001-004	Erythema	12/22/17	3.0×10^{11}
003-002	Shortness of breath	12/06/17	1.0×10^{11}

Dose Limiting Toxicities

There have been no dose-limiting toxicities reported in the IND treated patients and no drug related events of any grade in the compassionate use treated patients.

Progression

To date, none of the SNS-301 treated patients have experienced disease progression. Table 4 lists the patients and their current progression free interval.

Table 4: : Progression Free Intervals

Patient ID	IND Study (Y/N)	Primary Cancer	Date of First Dose	Progressive Disease (Y/N)	Current Progression Free Interval (months)
001-001	Yes	Prostate	1/5/17	No	> 15
004-001	Yes	Prostate	4/19/17	No	> 11
004-002	Yes	Prostate	5/23/17	No	> 11
004-004	Yes	Prostate	6/20/17	No	>10
004-003	Yes	Prostate	7/18/17	No	>9
003-002	Yes	Prostate	7/25/17	No	>9
001-003	Yes	Prostate	8/21/17	No	>8
003-006	Yes	Prostate	11/13/17	No	>5
004-006	Yes	Prostate	11/20/17	No	>5
004-007	Yes	Prostate	11/29/17	No	>5
001-004	Yes	Prostate	12/20/17	No	>4
003-007	Yes	Prostate	1/29/18	No	>3

Conclusion

While still early in the study, these data taken together suggest that SNS-301 is well tolerated, does not result in local injection site reactivity, and does not appear to result in dose limiting toxicities or metabolic complication.

3.4 Study Rationale

Oncology trials frequently employ dose-escalation using a 3+3 schema; it is considered standard practice for determining the MTD of a particular study treatment in humans. The starting dose for such studies is usually calculated from the results of toxicology studies, which are often not performed in humans [8]. In this study, the starting dose and the subsequent dose escalations were determined from the results of a repeated dose toxicology study conducted in rats that evaluated the same 3 intradermal doses and dose frequency for the SNS-301 as proposed here. Only minimal toxicologic effects were observed in the animals at the higher two dose levels and these were resolved through the 2- and 4-week recovery periods (see Section 3.2).

The selection rationale for the specific dose levels proposed for this study is based on the in vivo results of this range of doses in mice and rats that have shown both immunogenicity and efficacy of the SNS-301 vaccine. The vaccine has demonstrated immunogenicity in rats by IgG antibody response to recombinant HAAH and to the recombinant bacteriophage HAAH-1λ drug substance at each dose level, 2×10^{10}, 1×10^{11} and 3×10^{11} particles. This antibody response is both dose level-dependent and dose number-dependent. In mice, dose levels of approximately 2×10^{10} to 3×10^{11} particles have also demonstrated immunogenicity in a similar dose level- and dose number-response manner in multiple studies. Furthermore, SNS-301 vaccine doses up to 3×10^{11} particles have demonstrated inhibition of solid tumor growth and metastases in in vivo mouse tumor models with the mouse hepatocellular carcinoma cell line, BNLT3, and with the mouse breast cancer cell line, 4T1 and have demonstrated inhibition of metastases in a rat tumor model with the rat prostate cancer cell line, MLLB-2.

The dose-escalation phase will be conducted in patients with biochemically relapsed prostate cancer because this is a cancer that generally takes a long time to develop. Further, archived patient tumor tissue will be tested for the HAAH epitope before enrollment into the study; patients who do not test positive for the HAAH epitope in archived tissue or fresh serum

sample will not be entered into the treatment phase as they are not deemed suitable candidates for the HAAH vaccine. The 21-day treatment phase will allow the patient sufficient time to recover from any adverse effects of the vaccine before the next dose. It is anticipated that the SNS-301 will lead to the development of active anti-HAAH immunity with consistent polyclonal anti-HAAH antibody titers in addition to development of anti-HAAH T-cells. This is further supported by our current data from patients treated up to now. Based on this, a decision has been made to limit the total number of injections to 9, which accounts for 6 months of treatment with an additional 6 months of follow up, with monthly measurement of PSA levels and anti-HAAH immunity parameters. Patients who, at the time of this amendment, have received more than 9 injections, will cease treatment at the time of their last injection when this amendment goes into effect and will also be followed for 6 months, as will patients whose disease progression leads to treatment stoppage before 1 year. Patients with evidence of progression and declining HAAH immune parameters have the option of resuming therapy on the study protocol in the 6 month follow up period. All patients are eligible for enrollment in the expanded access protocol after study closure.

4. Study Objectives and Endpoints

4.1 Study Objectives

4.1.1 Primary

- To determine the maximum tolerated dose (MTD) of SNS-301 based on the incidence of dose-limiting toxicities (DLT) and the maximum administered dose of SNS-301, when administered every 21 days in patients with biochemically relapsed prostate cancer

4.1.2 Secondary

- To assess the overall safety of SNS-301

4.2 Study Endpoints

4.2.1 Primary

- To determine the MTD
- Determine the recommended Phase 2 dose (RP2D) if different than the MTD
- Determine the DLTs associated with SNS-301

4.2.2 Secondary

- Incidence of administration site reactions
- Biochemical safety and tolerability
- Geometric mean titers of anti-HAAH antibodies by dose
- Antigen-specific CTL responses by dose
- Production of B cell and T cell response of interest

4.2.3 Clinical secondary endpoints

- Change in the prostate-specific antigen (PSA) velocity
- Reduction in the PSA doubling time from pre-baseline

4.2.4 Pharmacodynamic secondary endpoints

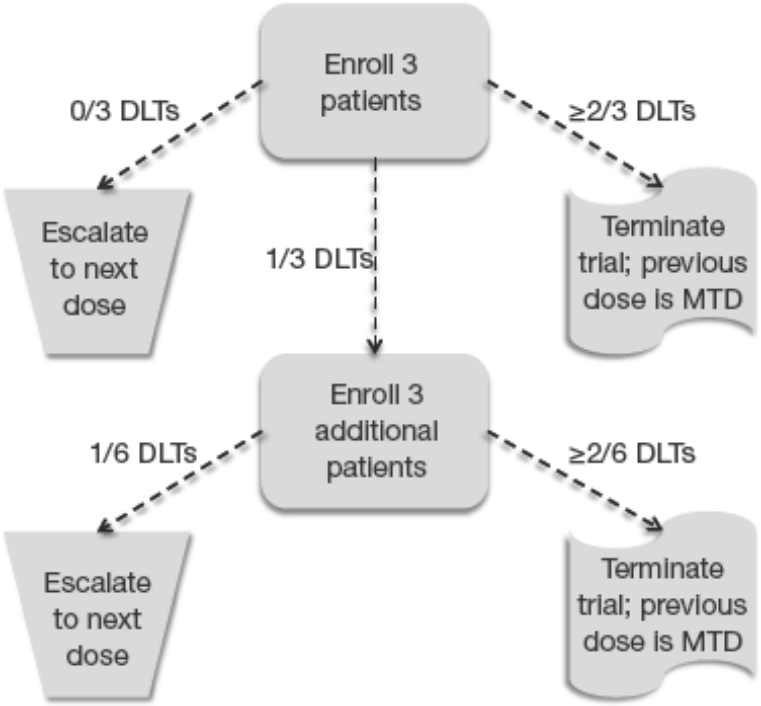
- Duration of antigen-specific anti-HAAH antibody titers
- Changes in the amplitude or duration of the production of anti-HAAH antibodies
- Correlation of anti-HAAH titers and serum HAAH levels

5. INVESTIGATIONAL PLAN

This is a Phase I, open-label, study of SNS-301, an HAAH-directed nanoparticle vaccine, given intradermally in cohorts of patients with biochemically relapse prostate cancer, using a fixed dose-escalation schema every 21 days to establish the MTD.

5.1 Overall Study Design and Plan Description

Figure 1: Dose-escalation study design (3+3 schema)



Following informed consent and screening, archived prostate tumor tissue and patient serum will be tested for the expression of HAAH. Patients who test positive for HAAH expression in either archived tumor tissue or fresh serum may be continued in the study. Baseline biochemical testing (chemistry, complete blood count [CBC], coagulation panel, CH50, and PSA) will be obtained prior to study treatment administration.

Treatment will consist of single repeated doses of SNS-301 administered every 21 days. A traditional 3+3 dose-escalation schema will be used to determine the MTD of SNS-301 for the first 2 doses and a modified dose-escalation schema with 6 patients per dose level for the remaining dose. Planned doses of SNS-301 are 2.0×10^{10}, 1.0×10^{11} and 3.0×10^{11} particles per administration diluted to 1 mL and administered intradermally. Additional patients will be enrolled at the highest dose level until at least 6 patients can be evaluated even if no DLTs are observed at the dose. Planned treatment may continue for two additional doses of SNS-301 administered every 21 days. Serum and whole blood samples will be obtained on the day of study treatment administration (Day 1) and 21 days thereafter. In patients who continue to receive study treatment, biochemical and immunologic testing will continue every 21 days.

The MTD will be determined over the first 21-day interval following a single dose of SNS-301 in 3 consecutive dose cohorts. The MTD will be considered the dose level lower than that

dose which produces ≥ 2 DLTs in 3 or 6 patients. A DLT will be considered a protocol-specified drug-related grade 3-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] V 4.03) adverse experience) (Section 5.4.5.1). The RP2D will be the highest dose administered if no MTD is observed.

Dose cohorts will be enrolled sequentially.

An evaluation period of at least 21-days for the first patient (sentinel patient) in a new cohort is required to evaluate tolerability before adding additional patients to the cohort. If safety/tolerability is adequate, then the remaining patients will be dosed in the cohort. A second evaluation will occur for the last patient of each cohort of at least 21-days to evaluate safety/tolerability before dose escalation to the next cohort will occur. Enrollment will be held if an administration site reaction (ASR) of grade 3 or greater (NCI-CTCAE V4.03) is observed until the event resolves. In the event enrollment is held for an ASR, the Sponsor, Medical Monitor and PI will evaluate the outcome of the ASR and must agree to continued enrollment.

Dose-escalation will proceed once all patients in a cohort (unless the MTD is observed) have completed a 21-day safety evaluation following the first dose of study treatment in the cohort. Planned treatment may continue for an additional 2 extra doses of SNS-301 administered every 21 days. Additional patients will be enrolled at the highest dose level until at least 6 patients can be evaluated even if no DLTs are observed at the dose In patients who tolerate SNS-301, additional treatment may be continued with single doses of SNS-301 at their current dose level, to maintain geometric mean titer (GMT) of HAAH antibodies to no less than 4 times the baseline value for at least six months (9 injections). Treatment will be terminated with the 9th injection or will otherwise be terminated at any time upon the observance of PSA doubling < 90 days or occurrence of unacceptable toxicity as determined by the Investigator (either for that patient or in their dose cohort). After termination, patients will be followed for an additional 6 months with monthly PSA levels and imaging studies as needed.

Once the MTD/RP2D is determined, patients receiving ongoing treatment may be escalated to that dose for subsequent treatments and receive a maximum of 9 injections. Patients who have received more than 9 injections due to the timing of the amendment limiting therapy to 6 months (9 doses), will be stopped at their last dose received and be followed for 6 months as with other patients. These subjects will continue to be followed for safety and biochemical PSA monitoring on a monthly basis for 6 months and are eligible to resume SNS-301 in case of increases in PSA doubling to < 90 days or other evidence of disease progression and decline in immunological parameters.

Pharmacodynamic:

Exploratory pharmacodynamic (PD) analysis will be performed using dose, vaccine-specific antibody response (geometric mean titer), antigen-specific T and B cell indices, and the relative expression of HAAH in each patient's tumor. The PD will be balanced and optimized to the degree of antigen-specific immune response and minimized for the production of regulatory immune processes.

Other Safety:

Safety endpoints will be evaluated by the incidence and severity of administration site reactions, changes in biochemical safety measures, general incidence and types of AEs, serious adverse events (SAEs), and other overt toxicities.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Signed and dated written Ethics Committee approved informed consent
2. Men aged 21 to 85 years with a histologic diagnosis of prostate cancer with a biochemical relapse following definitive local therapy (RP or radiation therapy)
3. Patients are not eligible or are unwilling to receive additional definitive therapy following relapse (either RP or radiation therapy)
4. No prior cytotoxic chemotherapy for the current cancer
5. Normal electrocardiogram (ECG) or ECG with no clinically significant findings as determined by the Principal Investigator
6. Presence of biochemically relapsed prostate cancer defined as either: 1) PSA > 2 ng/mL 1 year following initial definitive treatment for prostate cancer: or, 2) PSA doubling time (greater than 0.2 ng/mL) < 12 months; or, 3) PSA velocity > 2 ng/mL/year at any time following radical prostatectomy or radiation therapy.
7. Positive expression of HAAH in either archived tumor tissue (if available) or fresh serum
8. No clinical or radiologic evidence of distant metastatic disease as measured by pelvic MRI or CT scan in addition to bone scan. These studies will need to be performed within 56 (+ 7 days) days prior to the start of the study.
9. No history of immunosuppressive disease
10. No evidence of active autoimmune disease. Active autoimmune disease is defined as any disease process that has specifically needed administration of immune suppressive and or cytoreductive therapy currently or within the last 1 year.
11. Able and willing to comply with all study procedures

5.2.2 Exclusion Criteria

1. PSA doubling time of < 3 months
2. Participation in a clinical trial within 30 days prior to enrollment
3. Prior major surgery or radiation therapy within 4 weeks of enrollment
4. Any illness or condition that in the opinion of the Investigator may affect the safety of the patient or the evaluation of any study endpoint
5. Screening blood counts of the following:
   Hematopoietic:
   Absolute neutrophil count $\leq$ 1500/μL,
   Platelets $\leq$ 100,000/μL,
   Hemoglobin $\leq$ 9 g/dL;
   Liver/Metabolic:
   Alanine aminotransferase (ALT) and aspartate transaminase (AST) $\geq$ 2.5 × ULN range,
   Total bilirubin $\geq$ 2 × ULN,
   Albumin $\leq$ 2.8 g/dL;
   Renal:
   Creatinine clearance $\leq$ 50 mL/min as predicted by the Cockcroft-Gault formula
6. Subjects whose partners are WOCBP must use an adequate method of birth control while on study drug and at least for 3 weeks after discontinuation of study drug

7. Current or anticipated concomitant immunosuppressive therapy (excluding non-systemic inhaled, topical skin and/or eye drop-containing corticosteroids)
8. Any concurrent condition requiring the continued use of systemic steroids (see above) or the use of immunosuppressive agents including methotrexate. All other systemic corticosteroids must be discontinued at least 4 weeks prior to first study treatment
9. Receipt of any blood product within 1 month of enrollment
10. Receipt of any vaccine within 4 weeks of enrollment
11. Active drug or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements
12. Been imprisoned or compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness
13. Patients who have a history of coagulopathies, thrombosis or who are receiving active anticoagulation for any condition, such as but not limited to, artificial heart valves, atrial fibrillation, etc.
14. Any other conditions judged by the Investigator that would limit the evaluation of a subject

5.2.3 Removal of Patients from Treatment or Assessment

The patients may withdraw from treatment with study product if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision to protect the safety of the patient. All efforts should be made to document the reason for discontinuation and this should be documented in the electronic case report form (eCRF).

Other criteria for possible discontinuation are:

- PSADT < 90 days
- Unacceptable toxicity as judged by the Principal Investigator

Adverse events which are dose-limiting toxicities

Patient is lost to follow-up

Patients will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of a followed-up AE, or the initiation of post study treatment, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the 'end of study'.

The patients may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision:

Patients who are lost to follow-up:

The Investigator should make every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (e.g. times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up.

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

5.2.4 Enrollment Holds

Enrollment will be held if the subject experiences a grade 3 or greater ASR as determined by the Investigator. The subject must be withdrawn from the study if they experience a grade 3 ASR. Enrollment can be re-started after agreement between the Principal Investigator, Medical Monitor, and the Sponsor.

Study enrollment will be halted in the event of a death of a subject while on the study or within a 30-day period follow study drug exposure regardless of drug relationship. In the event the enrollment is halted, a clinical review of the subject case will be made by the Principal Investigator, Medical Monitor, and the Sponsor to assess the safety of the medicinal product. If the review concludes there is no association of the death with the study drug, restarting enrollment may proceed.

5.3 Study Treatment

5.3.1 Treatments Administered

Subjects will be administered intradermally the SNS-301 doses of 2.0 x $10^{10}$and 1.0 x 10^{11} particles per administration according to the 3+3 dose-escalation schema described herein and for the 3.0 x 10^{11} particles per administration dose additional patients will be enrolled until at least 6 patients can be evaluated even if no DLTs are observed at the dose. Planned treatment may continue of additional doses of SNS-301 administered every 21 days.

5.3.2 Identity of the Study Treatment

5.3.2.1 Study Treatment Details

The HAAH Nanoparticle Vaccine drug substance is a recombinant bacteriophage lambda construct that is engineered to display a fusion protein of phage gpD and a portion of the HAAH protein sequence. The HAAH-1λ (SNS-301) construct contains 199 amino acids from the N-terminal region (amino acids 113 – 311) of the molecule.

The drug substance is characterized by testing that includes appearance, pH, and identity by dot blot using HAAH-specific monoclonal antibody, impurities (bioburden, endotoxin, host cell protein), determination of size distribution by particle analysis, quantitation by particle analysis, protein determination and potency by antigen enzyme-linked immunosorbent assay (ELISA).

5.3.2.2 Study Treatment Administration

The vaccine will be delivered intra-dermally by a single-use 3M® hollow microstructured transdermal system (hMTS) device.

5.3.2.3 Handling and Storage of Study Treatment

5.3.2.3.1 Packaging and labeling

The study treatment, SNS-301, will be packaged by the Sponsor, and supplied in an open-label basis.

The supplies will be labeled as follows:

- Sponsor’s name and address

- Study number
- Content of the vial
- Dosing instructions
- Batch Number
- "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

5.3.2.3.2 Storage

The study drug product is stored at 2 – 8 °C. Temperature excursions to ≤25°C for less than 24 hours are acceptable.

5.3.2.4 Handling/Responsibilities

The study Treatment administrator must store and administer the study treatment according to the instructions provided by the Sponsor.

All study treatments shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of study treatment issued and returned is maintained.

Any quality issue noticed with the receipt or use of a study treatment (deficiency in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply study treatment to a third party, allow the study treatment to be used other than as directed by this Clinical Trial Protocol, or dispose of study treatment in any other manner.

5.3.2.5 Study Investigational Treatment Management and Disposal

All unused study treatments should be discarded at the investigational site and a destruction certificate obtained. The study treatment Administrator will submit the copy of Product Accountability Log to the Sponsor.

A potential defect in the quality of the study treatment may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall study treatment and eliminate potential hazards.

5.3.3 Method of Assigning Patients to Study Groups

This is an open-label dose-escalation study; no randomization will occur.

All patients who sign the informed consent form (ICF) will be assigned a patient study number. Patient eligibility must be verified by the Investigator. If a patient fails to meet an eligibility criterion during the screening period, then the Investigator will complete a screening failure form in the e-CRF.

The study treatment will be administered only to patients included in this study following the procedures set out in this clinical study protocol. Details of the exact time of administration of medication (day/month/year, hour:minute) and the labeling on SNS-301 vials will also be documented in the e-CRF.

Patient withdrawn from the study retain the same patient number. New patients must always be allotted a new patient number.

5.3.4 Selection of Doses for the Study

This is an open-label study. Sequential cohorts will be enrolled in the order they present. In the dose-escalation cohorts, 3 or 6 patients will be treated with successively higher doses of SNS-301: 2.0×10^{10}, 1.0×10^{11} and 3.0×10^{11} particles every 21 days.

5.3.5 Selection and Timing of Dose for Each Patient

The MTD will be determined over the first 21-day interval following a single dose of SNS-301 in 3 dose cohorts. The MTD will be considered the dose level lower than that dose which produces ≥ 2 DLT.

Dose-escalation will proceed when once all patients in a cohort (unless the MTD is observed) have completed a 21-day safety evaluation following the first dose of study treatment in the cohort. Multiple patients can be in screening phase simultaneously, but the first eligible patient able to be treated will be assigned the next treatment slot that is available for study.

More specifically, the first patient of each dose level will be enrolled and assessed for DLTs during cycle 1. Subsequent patients in a cohort can be enrolled after a 21-day review for tolerability by the Medical Monitor, Sponsor and Investigator(s) has been completed in the first patient.

After evaluation of the safety data of 3 patients in cycle 1 of the 2.0×10^{10} particles per administration dose, if none of the first 3 patients experiences a DLT, then dose-escalation to the next level (1.0×10^{11} particles per administration) can occur. When one patient shows a DLT, an additional 3 patients will be enrolled at the same dose level. If no more than 1 out of 6 patients experiences a DLT, patient enrollment to the next dose level can start.

Patients who withdraw from the study during cycle 1 (Day 1 – Day 22 pre-dose) for reasons other than safety or toxicity will be replaced.

Subsequent dose-escalation will be conducted in the same manner.

If the MTD is not achieved at the dose level of 3.0×10^{11} particles per administration, further dose-escalation will not be conducted. Additional patients will be enrolled at the highest dose level until at least 6 patients can be evaluated even if no DLTs are observed at the dose.

Although the dose-escalation process is guided by the safety evaluation during cycle 1, the global safety profile of SNS-301 at each dose level will be considered and discussed with the Investigator before increasing doses.

Planned treatment may continue for additional doses of SNS-301, administered every 21 days.

In patients who tolerate SNS-301, additional treatment may be continued with single doses of SNS-301 at their current dose level every 21 days, to maintain geometric mean titer (GMT) of HAAH antibodies to no less than 4 times the baseline value for at least six months (9 injections).

Treatment will be terminated with the 9th injection or will otherwise be terminated at any time upon the observance of PSA doubling < 90 days or occurrence of unacceptable toxicity. After termination, patients will be followed for an additional 6 months with monthly PSA levels and imaging studies as needed.

Once the MTD/RP2D is determined, patients receiving ongoing treatment may be escalated to that dose for subsequent treatments and receive a maximum of 9 injections. Patients who have received more than 9 injections due to the timing of the amendment limiting therapy to 6 months (9 doses), will be stopped at their last dose received and be followed for 6 months as with other patients. These subjects will continue to be followed for safety and biochemical PSA monitoring on a monthly basis for 6 months and are eligible to resume SNS-301 in case

of increases in PSA doubling to < 90 days or other evidence of disease progression and decline in immunological parameters.

5.3.5.1 Dose-limiting toxicities

Any of the following, if judged to be associated with SNS-301 (i.e., possibly-, probably-, or definitely related to), will be considered a DLT which are based on the NCI-CTCAE V4.03 criteria:

1) Grade 4 non-hematological toxicities (excluding alopecia) of any duration
2) Grade 3 non-hematologic (non-laboratory) toxicity lasting > 3 days despite optimal supportive care
3) Any Grade 3 or Grade 4 non-hematologic laboratory value if: a). Medical intervention is required to treat the subject; b), the abnormality leads to hospitalization; c). The abnormality persists for >1 week.
4) Grade 4 hematologic toxicity, other than those specified in criteria 5 and 6 below, lasting > 7 days
5) Grade 3 or Grade 4 febrile neutropenia of any duration
6) Grade 3 thrombocytopenia in combination with a grade 3 or greater blood and lymphatic system disorder
7) Grade 3 AST or ALT that is associated with a grade 2 rise in bilirubin

5.3.5.2 Dose delay or reduction

In case of non-DLT AE (grade 2 NCI-CTCAE V4.03 drug related AE), the dosing interval of 3 weeks can be extended to up 42 days to allow the recovery from a related toxicity and the patient will resume at the same dose. If the patient experiences the same toxicity requiring a dose-delay at the subsequent cycle, the patient should be discontinued.

No sentinel safety assessment will be made; however, enrollment will be controlled so that a 21-day observation period is completed on the first subject in each cohort before any further enrollment is performed. Additionally, enrollment will be held if an ASR of grade 3 or greater is observed until the event resolves. In the event enrollment is held for an ASR, the Sponsor and PI will evaluate the outcome of the ASR and must agree to continued enrollment.

5.4 Blinding

This was an open-label study, so there will be no blinding of study personnel.

5.4.1 Prior and Concomitant Treatment

All treatments being taken by the patients at entry to the study or at any time during the study in addition to the study treatment are regarded as concomitant treatments and must be documented in the appropriate screen of the e-CRF.

5.4.1.1 Allowed concomitant treatments

The following concomitant treatments are permitted during this study:

- Supportive treatment will be given as medically indicated.
- Prophylactic antiemetic premedication including corticosteroids and 5-hydroxytryptamine 3 antagonists.

5.4.1.2 Prohibited Medications or Treatments During Study

Medications such as those listed below are not permitted in the course of the trial:

- Concurrent treatment with other investigational drugs
- Concurrent treatment with any other anticancer therapy including radiotherapy

5.4.2 Study Treatment Accountability and Compliance Procedures

Administration of the study treatment will be supervised by the Investigator or sub-Investigator. The study treatment should not be destroyed until the site is contacted by the Sponsor to provide disposition details. The person responsible for drug dispensing is required to maintain adequate records of the study treatment. These records (e.g., product accountability log) include the date the study treatment is received from the Sponsor and administered to the patient.

The person responsible for study treatment administration to the patient will record precisely the date and the time of the study treatment administration.

5.5 Safety and Efficacy Variables and Study Assessments

Flow charts for the study assessments are provided in Table 1.

5.5.1 Pre-study Assessments

5.5.1.1 HAAH expression of archived tissue

After patient consent is given, archived tumor tissue (if available) and serum will be tested for the expression of HAAH. Patients who test positive may be enrolled into the study.

5.5.1.2 HAAH expression in serum

After patient consent is given, patient serum will be tested for the expression of HAAH (Section 7.5.3.2). Patients who test positive will be enrolled into the study.

5.5.2 Study visits and assessments

The following evaluations will be performed. All procedure dates defined are based on the duration (days) from the initial dose of study medication.

5.5.2.1 Screening period (Day -56 (+ 7 days) to Day 0)

Following patient informed consent, archived prostate tumor tissue and patient serum will be tested for the expression of HAAH. Only patients who test positive for HAAH expression in archived tumor tissue (if available) or fresh serum may be continued in the study. If tumor tissue or fresh serum is initially negative for HAAH, the patient can be re-screened for the study if PSA level have increased over the next 6 months, patient is willing to participate on study in the future, and HAAH expression is now positive in serum or tumor tissue (on retest). If archived tumor tissue is negative on initial testing, the same tumor tissue will not be re-tested.

Assessments at Screening:

- Informed consent administered
- HAAH expression in archived tumor tissue (if available) and/or fresh serum
- Medical/oncology history, demographics
- Baseline signs and symptoms
- Physical examination, vital signs, ECG

- Eastern Cooperative Oncology Group (ECOG) performance score
- Prostate-specific antigen (PSA) assessment: if the screening period is between 3 and 8 weeks prior to first dose, the PSA must be re-tested within 14 days prior to first dose
- Clinical laboratory tests, chemistry, hematology, coagulation, CH50 if the screening period is between 3 and 8 weeks prior to first dose, the labs noted must be re-tested within 14 days prior to first dose
- Pelvic MRI or CT scan in addition to bone scan.

5.5.2.2 Dose-escalation Treatment: Day 1

- Immunologic blood collection – pre-dose on day of drug administration (eg Day 1) and 21 days thereafter.
- Medical/oncology history review
- Symptom-directed physical examination
- Prostate-specific antigen (PSA) assessment
- Vital signs, ECG
- ECOG score
- Baseline biochemical testing (chemistry, CBC, coagulation, CH50,) prior to study drug administration
- Study treatment administration
- Physician administration site assessment (post administration)
- Adverse events and concomitant medications

5.5.2.3 Dose-escalation Treatment: Day 8 ± 2 days

- Symptom-directed physical examination
- Vital signs
- ECOG score
- Biochemical testing: chemistry, hematology, coagulation, CH50
- Physician administration site assessment
- Adverse events, concomitant medications

5.5.2.4 Dose-escalation Treatment: Day 15 ± 2 days

- Symptom-directed physical examination
- Vital signs
- ECOG score
- Clinical laboratory tests, chemistry, hematology, coagulation, CH50
- Adverse events, concomitant medications

5.5.2.5 Study Visits: Day 22, Day 43 ± 3 days

- Immunologic blood collection – pre-dose on day of drug administration on Day 22, 43, and every 21 days thereafter if continuing treatment
- Symptom-directed physical examination
- Vital signs and ECG
- Eastern Cooperative Oncology Group (ECOG) performance score
- Prostate-specific antigen (PSA) assessment
- Biochemical testing: chemistry, hematology, coagulation, CH50
- Evaluation of subject to allow continued dose escalation
- Study treatment administration
- Physician administration site assessment (post-administration)
- Adverse events and concomitant medications

5.5.2.6 Additional treatment: Every additional 21 days ± 3 days if indicated

A maximum of 9 drug administrations will be administered on this study for all patients, except in the case of progression on study and or in the case of patients who had been on study for more than 6 months at the time of this amendment. Patients with evidence of progression and declining HAAH immune parameters within 6 months of stopping therapy have the option of resuming therapy on the study protocol.

- Immunologic blood collection – pre-dose on day of drug administration every 21 days thereafter if continuing treatment.
- Symptom-directed physical examination
- Vital signs and ECG
- Eastern Cooperative Oncology Group (ECOG) performance score
- Prostate-specific antigen (PSA) assessment
- Biochemical testing: chemistry, hematology, coagulation, CH50
- Study treatment administration
- Physician administration site assessment (post-administration)
- Adverse events and concomitant medications

5.5.2.7 Follow up and End of Study (EOS): 28 days ± 3 days after last treatment for a total of 6 months

- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) performance score
- ECG
- Prostate-specific antigen (PSA) assessment
- Clinical laboratory tests, chemistry, hematology, coagulation, CH50 (only on first follow up)
- Immunologic blood collection
- Adverse events and concomitant medications

5.5.3 Safety Measurements

5.5.3.1 Clinical Laboratory Assessments

Hematological toxicities will be assessed in term of hemoglobin value, white blood cell, neutrophil, platelet and, lymphocyte count according to NCI-CTCAE V4.03 AE grading.

Laboratory abnormalities (grade 1 and greater that are listed in the NCI-CTCAE V4.03) should be recorded on the AE page regardless of their causality. Test analytes are provided in the table below.

Hematology	Serum chemistry
Full and differential blood count Hematocrit (Hct) Hemoglobin (Hgb) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Blood Urea Nitrogen (BUN) or Urea Carbon dioxide (CO_2) Creatinine Electrolytes (Na, K, Cl, Ca, P) Glucose (either fasting or non-fasting) Lactate dehydrogenase (LDH) Total bilirubin Direct bilirubin Total cholesterol Triglycerides

Coagulation, CH50	PSA
Prothrombin time (PT)/INR Activated partial thromboplastin time (PTT)	PSA

5.5.3.2 Immunological blood collection

Antigen-specific anti-HAAH antibody titers

Anti-HAAH antibody titers from serum samples are determined by ELISA. Patient sera are serially diluted and incubated in microplate wells coated with recombinant HAAH antigen. The plates are then incubated with anti-human immunoglobin G (IgG)-peroxidase conjugate, followed by color development to detect the amount of patient IgG bound to the HAAH antigen. The data are expressed as the reciprocal of the end-point titer.

Antigen-specific CTL responses

Cytotoxic T-cells (CTLs) and APC will be isolated from patient peripheral blood monocytes (PBMCs) by magnetic activated cell sorting (MACS) on the basis of specific cell surface markers. APCs will be loaded with antigen (HAAH) for 3 hours and labeled with a fluorescent dye, carboxyfluorescein succinimidyl ester (CFSE), and incubated with CTLs at varying effector to target cell ratios. Cell-mediated cytotoxicity is determined by antigen-specific release of dye.

Cytotoxic T-Lymphocyte Killing Assay

Quantitation of specific cell lysis by patient-derived CD8+ T-cells will be determined using a flow cytometric assay employing two fluorochromes, 5- (and 6-) carboxyfluorescein diacetate succinimydyl ester (CFSE) and 7-amino actinomycin D (7-AAD). CFSE is pre-loaded into target cells where upon internalization it is covalently linked to intracellular amine groups and thus does not leach from cells into the media nor is it transferred to adjacent cells. As such, CFSE can be used as a marker to differentiate between effector and target cells in the final assay. 7-AAD is a membrane impermeable dye that when added subsequent to the period of cell lysis can only be incorporated only into dead cells (whose membranes have been compromised) and thus can be used to differentiate between live and dead cells.

Target Cells: Patient derived antigen presenting cells (APCs) will be isolated from peripheral blood mononuclear cells (PBMCs) using magnetic assisted cell separation (MACS) technology (Miltenyi Biotec). APCs may be loaded with antigen (HAAH) for 12-16 hrs. prior to use in the CTL assay. Immediately prior to assay, target cells will be loaded with CFSE.

Effector Cells: CD8+ T-cells will be isolated from peripheral blood mononuclear cells (PBMCs) using magnetic assisted cell separation (MACS) technology (Miltenyi Biotec).

Lysis: Effector and target cells will be co-incubated at varying effector to target cell ratios at 37^0C for 4 hours. Target cells are held constant at ~25,000 cells per well of a 96 well plate while effector cells will be varied from a ratio of 1:1 with target cells up to 25:1. After incubation, cells are labeled with 7-AAD to differentiate between live and dead cells. Cells are subsequently analyzed by flow cytometry four staining populations are counted: those that stain with both CFSE and 7-AAD, those that stain with CFSE but not 7-AAD, those that stain with 7-AAD but not CFSE and those that do not stain with either fluorophore. Percent specific lysis is determined by taking the ratio CFSE/7-AAD labeled cells to total CFSE labeled cells. The ratio of non-CFSE labeled cells vs. CFSE labeled cells is an indicator of the true effector to target cell ratio.

Measurement of B cell and T cell response

B cells will be isolated from patient PBMCs by magnetic activated cell sorting (MACS) on the basis of specific cell surface markers. After several days of growth in culture, medium will be tested for antigen-specific anti-HAAH antibody titers as above.

CD4+ T-cells responses will be determined by isolating CD4+ T-cells and APC from patient PBMCs by magnetic activated cell sorting (MACS) on the basis of specific cell surface markers. APCs will be loaded with or without antigen (HAAH) for 3 hours and coincubated with CD4+ T-cells overnight. Antigen-specific T-cell activation will be determined by flow cytometric measurement of CD154 and interferon γ.

Measurement of CD4, CD8, CD19 cell populations

CD4+, CD8+ and CD19+ cell populations as a percentage of total PBMCs will be determined by flow cytometry.

5.5.3.3 Administration site reaction

The area around the administration site will be assessed by the physician for adverse reactions at least 30 minutes post study drug administration. The Investigator will grade any ASRs according to the NCI-CTCAE V4.03 (excluding the actual expected micro-injection punctures).

Patients will be required to report any change in the administration site and return to the clinic for evaluation by the Investigator.

5.5.3.4 ECOG performance score

The health, activity and well-being of the patient was measured by the ECOG performance status and was assessed on a scale of 0 to 5 with 0 being fully active and 5 being dead. Full details are described in Appendix A.

5.5.3.5 Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related and occurs after the patient is given the first dose of study drug. Any AE that occurs prior to the first dose is part of the medical history.

At least 30 minutes post dose, the Investigator should evaluate the site of drug administration and query the patient in a general manner regarding the presence of any untoward effects.

Laboratory abnormalities (grade 1 and greater that are listed in the NCI-CTCAE V4.03) should be recorded on the AE page regardless of their causality. Worsening of a pre-existing condition is also considered an AE as is the discovery of an abnormal finding during physical exam that was not included in the medical history.

Patients will be encouraged to spontaneously report any AE. Study personnel will ask open-ended questions to obtain information about AEs at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented.

Causality

Events will be considered treatment related if classified by the Investigator as possible, probable, or definitely associated with the use of the drug. Association of events to the study treatment will be made using the following definitions:

Term	Definition
Definitely Not	The event is definitely not associated with study treatment.
Probably Not	The temporal association, patient history, or clinical condition is such that the study treatment is not likely to have had an association with the observed event.
Possible	The event: a) follows a reasonable temporal association with the study treatment administration, but b) could have been produced by the patient's clinical condition or other therapy.
Probable	The event: a) follows a reasonable temporal association with the study treatment, b) abates upon discontinuation of study treatment, and c) cannot be reasonably explained by the patient's clinical condition or other therapy.
Definite	The event: a) follows a reasonable temporal association with the study treatment, b) abates upon discontinuation of study treatment, c) cannot be reasonably explained by the patient's clinical condition or other therapy, and d) reappears on re-exposure to the study treatment.

Severity

Signs and symptoms will be graded by the Investigator using the NCI-CTCAE V4.03 graded 1-5. Grade refers to the severity of the AE. For events not described in the NCI CTCAE, the Investigator will assign grades as 1= mild, 2=moderate, 3=severe, 4=life-threatening, and 5=fatal based on this general guideline:

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 ADL*

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE. (Grade 5 (Death) may not appropriate for some AEs and therefore may not an option.)

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.5.3.6 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an AE that:

- Is fatal
- Is life-threatening, meaning the patient was, 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 serious form or progressed, might have caused death
- Is a persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Requires or prolongs inpatient hospitalization
- Is a congenital anomaly or birth defect

Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed (# 1-5 above) in this definition.

All SAEs, including death due to any cause, that occur during this study and until 30 days after the last dose of study treatment, whether or not expected and regardless of causality, must be reported to the Medical Monitor immediately upon discovery of the event, using an SAE Form.

The Medical Monitor will advise the Investigator regarding the nature of any further information or documentation that is required. The Investigator should provide the following documentation at the time of notification if available:

- SAE Form
- AE (CRF) page
- Concomitant and support medication pages
- Relevant diagnostic reports
- Relevant laboratory reports
- Admission notes
- Hospital discharge summary (when available).

The Sponsor must notify FDA and all participating Investigators (i.e., all Investigators to whom the Sponsor is providing drug under its INDs or under any Investigator's IND) 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 under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of 21CFR 312.32. The Sponsor must identify all IND safety reports previously submitted to

FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Serious and unexpected suspected adverse reaction

The Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Submission of IND safety reports

The Sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The Sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the Sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

5.5.3.7 Unexpected fatal or life-threatening suspected adverse reaction reports

The Sponsor must also notify 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.

5.5.3.8 Clinical Laboratory Assessments

Hematological toxicities will be assessed in term of hemoglobin value, white blood cell, neutrophil, platelet, and lymphocyte count according to the NCI-CTCAE AE grading.

Laboratory abnormalities (grade 1 and greater that are listed in the NCI-CTCAE V4.03) should be recorded on the AE page regardless of their causality.

5.5.4 Efficacy (Clinical) Measurements

5.5.4.1 PSA assessment

Rising levels of PSA in serum are associated with prostate cancer [9]. Currently, PSA testing of serum is a standard test for indicating further investigation for prostate cancer.

A cutoff of 4.0 ng/mL has a sensitivity of 67.5-80% for detecting prostate cancer [10].

5.5.4.2 Treatment Failure

Treatment failure will be assessed by the observance of PSA doubling less than 90 days or unacceptable toxicity as determined by the Investigator.

5.6 Data Quality Assurance

At the study sites, all CRFs will be manually reviewed for completeness by the Sponsor's Clinical Research Associates. Site Staff will enter the required subject data into the provided Code of Federal Regulations (CFR) Part 11-compliant electronic data capture (EDC) system. Programmed computer edit checks will be run against the database to check for discrepancies and plausibility of the data. All issues resulting from the computer-generated checks will be resolved according to the Sponsor's standard data management practices in conjunction with the medical monitor, clinical study personnel, and the study Investigators.

6. Statistical Methods and Determination of Sample Size

6.1 Statistical and Analytical Plans

No formal statistical analysis will be performed, however, statistical derivation of all data will be derived by dose cohort and displayed for inspection.

For the dose-escalation phase of the study, cohorts of 3 or 6 patients will be screened, registered and treated at each dose level. The actual sample size may vary depending on the incidence of DLT during Cycle 1 at a given dose level. Once the MTD/RP2D is determined, additional patients may be accrued to provide for 6 patients in the MTD cohort. Approximately, 18 patients will be screened, registered and treated in the trial.

The primary safety analysis will assess MTD and AEs, clinical laboratory tests, and tolerability, based on the combined evaluation of immunogenicity and incidence of DLTs in each patient.

6.2 Determination of Sample Size

Cohorts of 3 or 6 patients will be screened and treated at each dose level. The actual sample size may vary depending on the incidence of DLT during the first cycle at a given dose level. Approximately 18 patients will be included and treated in the trial.

7. Ethics

7.1 Institutional Review Board (IRB) / Ethics Committee

Before the start of the study, the study protocol, ICF, and/or other appropriate documents will be submitted to the IRB, in accordance with local legal requirements. It is the responsibility of the Investigator to ensure that all aspects of the IRB review are conducted in accordance

with current local and U.S. regulations. Sensei and the Investigator must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled at the study site.

7.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles of the current version of the Declaration of Helsinki. The Sponsor and Investigator will comply with their responsibilities as defined in 21 CFR 312.50-312.70 and International Conference on Harmonization Guidance for Industry: E6 Good Clinical Practice (April 1996).

7.3 Patient Information and Consent

The Investigator will obtain informed consent from each patient enrolled in the study, in accordance with the U.S. Food and Drug Administration (FDA) regulations 21 CFR 50.20 - 50.27 and the laws and regulations of the state in which the investigation is being conducted.

The IRB must approve the ICF to be used by the Investigator. It is the responsibility of the Investigator to ensure that informed consent is obtained from the patient or his/her guardian or legal representative before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic, screening, or therapeutic procedures and the administration of the first dose of study treatment. The draft version of the ICF will be modified by each site and reviewed and approved in writing by Sensei prior to submission to the IRB. The terms of the consent and when it was obtained must also be documented in the patient's CRF. A second copy of the current ICF will be reviewed and signed by the patient to allow for patient re-screening on study if archived tumor tissue or fresh serum is initially negative for HAAH. Over this 6-month interval, PSA levels can be obtained and if they have increased appreciably from the original screening visit and HAAH is positive in serum or tumor tissue, the patient may be enrolled in the study. The same archived tumor tissue will not be retested.

Should a protocol amendment be made, the subject ICF may be revised to reflect the changes of the protocol. If the ICF is revised, it is the responsibility of the Investigator to ensure that an amended ICF is reviewed and approved by the IRB and signed by all subjects subsequently entered in the study.

7.4 Protocol Amendments

Neither the Investigator nor Sensei will alter this study protocol without obtaining the agreement of the other. Amendments will be made only in exceptional cases once the study has started at the discretion of Sensei with the agreement of the Investigator. Changes must be agreed to in writing, and signed, by all parties concerned. The changes then become part of the study protocol. Any changes in the protocol, even local/site requirements, will be written in an amendment. The IRB must be informed of amendments and, if necessary, approval must be sought for ethical aspects. Approval of amendments must also be obtained from the local regulatory authority, if necessary.

7.5 Confidentiality

All local legal requirements regarding data protection will be enforced. All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from Sensei. The anonymity of participating patients must be maintained. Throughout documentation and evaluation, the patients will be identified on CRFs and other documents submitted to Sensei

by their initials, birth date, and their patient number. Documents that are not to be submitted to Sensei, and that identify the patient (e.g., the signed ICF), must be maintained in confidence by the Investigator. The patients will be told that all study findings will be stored and handled in strictest confidence, according to local requirements. Patients will be informed that authorized research Investigators and agents of the FDA, other recognized regulatory authorities, and authorized representatives of the Sponsor, Sensei, have the right to inspect their medical records.

8. Investigators and Study Administrative Structure

This is a Phase 1 trial involving study centers located in the United States. The Investigator(s) responsible for the conduct of the study at their site, in compliance with this Protocol, are identified on the *Signature of Agreement Page* (Appendix B).

8.1 Sponsor Contacts

All questions regarding the enrollment of patients, regulatory requirements for the conduct of the study, safety reporting, or study conduct should be addressed to the Medical Monitor:

8.2 Data Handling and Recordkeeping

8.2.1 Electronic Case Report Form (eCRF)

Electronic case report forms will be provided via a Part 11 compliant database; patients will not be identified by name on any study documents. Each patient shall be identified by the patient identifying number that will be assigned by the Sponsor.

8.2.2 Maintenance of Study Records

The Investigator must retain a copy of all study documents, including reports to the IRB, regulatory authorities, and Sensei in accordance with FDA regulations.

The Investigator must maintain study documents:

- for a minimum of two years following the date the marketing application (NDA/BLA) is approved for the indication for which the drug was investigated; or,
- for a minimum of two years following the release date of the final report, if no marketing application is to be filed by Sensei, or if the marketing application is not approved for the indication for which the drug was investigated or is discontinued and the FDA has been notified; or,
- for a minimum of 15 years after the completion or discontinuation of the study to be filed in support of the registration in the European Union.

If the Investigator relocates, retires for any reason, or withdraws from the study, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or to Sensei. The Investigator must obtain Sensei's written permission before disposing of or transferring any records.

8.3 Final Report

Upon terminating the study, the Investigator will submit a final report to the IRB in keeping with local IRB regulations. This report should include any deviations from the protocol, the number and types of patients evaluated, the number of patients who discontinued, including reasons, results of the study, AEs, and a conclusion summarizing the results.

If requested by the Investigator, at the completion of the study and following analysis of the data, Sensei will supply a tabulated listing of data and a final clinical statistical report. A copy of the final study report and corrected CRFs, including a receipt to be returned to the Sensei Clinical Monitor, will be provided to each Investigator following its release by Sensei.

8.4 Publication and Use of Study Findings

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Sensei will prepare an *Integrated Clinical/Statistical Report*. Any publication/presentation of data must include the entire study population. Submission of data for publication/presentation will be coordinated and approved by Sensei in collaboration with the Investigator. Sensei will determine authorship of any publication by enrollment in consultation with the principal Investigator.

8.5 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local indemnification requirements. The civil liability of the Investigator, the persons instructed by him, the hospital, practice, or institute in which they are employed, and the liability of the Sponsor in respect of financial loss due to personal injury and other damage, which may arise as a result of the carrying out of this study, are governed by the applicable law. As a precautionary measure, the Investigator, the persons instructed by him and the hospital, practice or institute are included in such cover in regards to work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance. The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study. Such insurance is taken out by the Sponsor in accordance with regulations in the country concerned. To the extent that payments are made under such insurance, the right to claim damages from the Sponsor extinguishes.

9. REFERENCE LIST

1. Jia, S., W.J. VanDusen, R.E. Diehl, N.E. Kohl, R.A. Dixon, K.O. Elliston, A.M. Stern, and P.A. Friedman. 1992. cDNA cloning and expression of bovine aspartyl (asparaginyl) beta-hydroxylase. The Journal of Biological Chemistry 267:14322-14327.
2. Lavaissiere, L., S. Jia, M. Nishiyama, S. de la Monte, A.M. Stern, J.R. Wands, and P.A. Friedman. 1996. Overexpression of human aspartyl(asparaginyl)beta-hydroxylase in hepatocellular carcinoma and cholangiocarcinoma. The Journal of Clinical Investigation 98:1313-1323.
3. Shimoda, M., Y. Tomimaru, K.P. Charpentier, H. Safran, R.I. Carlson, and J. Wands. 2012. Tumor progression-related transmembrane protein aspartate-beta-hydroxylase is a target for immunotherapy of hepatocellular carcinoma. Journal of Hepatology 56:1129-1135.
4. De Berardinis, P., R. Sartorius, C. Fanutti, R.N. Perham, G. Del Pozzo and G. Guardiola. 2000. Phage display of peptide epitopes from HIV-1 elicits strong cytolytic responses in vitro and in vivo. Nature Biotechnology 18(8):873-876.
5. De Berardinis, P., L. D'Apice, A. Prisco, M.N. Ombra, P. Barba, G. Del Pozzo, S. Petukhov, P. Malik, R.N. Perham, and J. Guardiola. 1999. Recognition of HIV-derived B and T cell epitopes displayed on filamentous phages. Vaccine 17 (11-12):1434-1441.
6. Di Marzo Veronesse, F., A.E. Willis, C. Boyer-Thompson, E. Appella and R.N. Perham. 1994. Structural Mimicry and Enhanced Immunogenicity of Peptide Epitopes Displayed on Filamentous Bacteriophage: The V3 loop of HIV-1 gp120. Journal of Molecular Biology 243(2):167-172.
7. Perham, R.N., T.D. Terry, A.E. Willis, J. Greenwood, F. di Marzo Veronesse and E. Appella. 1995. Engineering a peptide epitope display system on filamentous bacteriophage. FEMS Microbiology Reviews 17(1-2):25-31.
8. Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. U.S. Department of Health and Human Services; Food and Drug Administration Center for Drug Evaluation and Research (CDER); July 2005, Pharmacology and Toxicology
9. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. Oct 8 1987;317(15):909-16
10. (http://emedicine.medscape.com/article/457394-overview#aw2aab6b8
11. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412–7420.
12. Stephenson, A., Kattan, M., Eastham, J., Dotan, Z., Bianco Jr, F., Lilja, H., and Scardino, P. 2006. Defining Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy: A Proposal for a Standardized Definition. J Clin Oncol 24:3973-3978.

10. LIST OF APPENDICES

Appendix	Title
A	Eastern Cooperative Oncology Group Performance Status (ECOG)
B	Principal Investigator Signature of Agreement Page

APPENDIX A: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

*As published in: *Am. J. Clin. Oncol*.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5:649-655, 1982.

APPENDIX B: PRINCIPAL INVESTIGATOR SIGNATURE OF AGREEMENT PAGE

INVESTIGATORS AGREEMENT

This document is a confidential communication of Sensei Biotherapeutics, Inc. (Sensei). The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written permission of Sensei. However, this document may be disclosed to appropriate Institutional Review Boards, ethics review committees, or authorized representatives of the Investigator or of boards of health under the condition that they are requested to respect the confidentiality of the document.

The signature of the Principal Investigator below constitutes his/her agreement to comply with the contents of this Protocol.

Principal Investigator's Name	Principal Investigator's Title
Principal Investigator's Address	
Principal Investigator's Signature	Date