WT2725 DOSING EMULSION
PROTOCOL D8350004

INITIAL PHASE 1 STUDY OF WT2725 DOSING EMULSION IN PATIENTS WITH ADVANCED MALIGNANCIES

IND No. 15,065

Version 7.0

3 Dec 2014

Incorporates Amendment 6

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1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: WT2725 Dosing Emulsion

Name of Active Ingredient: WT2725

Title of Study: Initial Phase 1 Study of WT2725 Dosing Emulsion in Patients with Advanced Malignancies

Study Center(s): Part 1: 4-8 clinical sites in the United States (US). Part 2: an additional 2 sites in the US may be included.

Phase of Development: 1

Study Objectives:

Primary:

The primary objectives are:

- to evaluate the safety and tolerability of WT2725 Dosing Emulsion
- to determine the maximum tolerated dose (MTD) of WT2725 Dosing Emulsion based on the evaluation of dose-limiting toxicity (DLT)

Secondary:

The secondary objectives are:

- to describe antitumor responses to WT2725 Dosing Emulsion based on the immune-related response criteria (irRC) (Wolchok-2009, Hoos-2010), modified International Working Group response criteria in acute myeloid leukemia (IWG) (Cheson-2003), and/or tumor markers
- to evaluate the immune responses to WT2725 Dosing Emulsion based on a series of circulating biomarkers in peripheral blood, delayed type hypersensitivity (DTH) to the WT2725 peptide, and immunohistochemistry in tumor tissue

Other:

The other objectives are:

- to evaluate immune response by level of Wilms' tumor gene product (WT1) protein expression in tumor cells
- to obtain blood serum for future retrospective analyses of additional biomarkers

Study Design: This is a Phase 1, open-label, dose-escalation, 2-part study in adult patients with advanced malignancies known to overexpress the WT1 protein. The study will primarily evaluate DLT and define the MTD of WT2725 Dosing Emulsion during the DLT Evaluation Period, which extends from the day of the first dose of study drug to just prior to the fifth dose (Days 1 - 29). In addition, antitumor activity and biomarkers indicative of immune response will be evaluated from the first dose until discontinuation of the patient from the study. An end of study assessment will take place within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy.

The initial patients in each dose escalation cohort will be enrolled at least one week apart to evaluate

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initial safety from the first 2 patients, then a "rolling-six" design will be employed that allows accrual of 2 to 6 patients concurrently in each dose escalation cohort.

In Part 1 of the study, the 0.3 mg cohort will be conducted first. After safety and tolerability have been established for the first cohort, enrollment of subsequent patients will be conducted sequentially in subsequent cohorts and continue until the MTD or all planned cohorts are attained. Enrollment of each cohort may include patients with any of the eligible tumor types (see below). Enrollment of the highest tolerable dose cohort (MTD or highest planned cohort) will continue until there are at least 6 patients total in the study with each tumor type that are evaluable for DLT, biomarkers, and response. This dose is considered the recommended phase 2 dose (RP2D). Enrollment of up to 3 RP2D cohorts of 10 patients each of a specific tumor type may take place at this dose in order to further characterize the safety and efficacy of WT2725 Dosing Emulsion at this dose in these subsets of patients. Additional dose escalation cohorts after the initial expansion cohorts may be enrolled if a MTD has not been determined and significant signs of toxicity have not been observed in the expansion cohorts.

In Part 2 of the study, the 18.0 mg cohort will be conducted first. After safety and tolerability have been established for the 18.0 mg cohort, enrollment of subsequent patients will be conducted sequentially in the 27.0 mg cohort. Approximately 10 patients at each dose level (18.0 and 27.0 mg) with at least 4 patients with each malignancy type (glioblastoma and acute myeloid leukemia [AML]) will be enrolled at each of these dose levels. If the MTD is reached in Part 2 before the total of 20 patients are enrolled, remaining patients will be enrolled at the prior dose level. In the event that a dose level is excluded from further study due to dose limiting toxicity all patients may continue the study at the most recently completed dose without DLT, eg, if the 27.0 mg dose is excluded due to DLT all patients may continue at 18.0 mg.

Patients who have completed the consolidation phase of their assigned cohort and have not experienced a DLT, ≥ Grade 2 study drug-related injection-site reaction, or required a dose reduction may have their dose escalated to that of the highest cohort for which safety and tolerability have been established. The expected time to enroll each dose escalation cohort (2 – 6 patients) is between 6 and 12 weeks.

Each part of the study will include 3 treatment phases based on intended timing of study drug dosing as indicated below:

Part 1:

- Vaccine Induction Phase: once every 7 days for 4 weeks (doses 1 - 5)
- Consolidation Phase: once every 14 days for 6 weeks (doses 6 - 9)
- Maintenance Phase: once every 28 days until discontinuation (dose 10 and thereafter)

Part 2:

- Vaccine Induction Phase: once every 7 days for 8 weeks (doses 1 - 9)
- Consolidation Phase: once every 14 days for 10 weeks (doses 10 – 15 [maximum of 6 doses])
- Maintenance Phase: once every 28 days until discontinuation (dose 16 and thereafter)

Number of Patients (planned): Approximately 60-80 patients total in Parts 1 and 2

Diagnosis and Main Criteria for Inclusion: Part 1: Adult patients with one of the following

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histologically or cytologically documented advanced stage malignancies: non-small cell lung, ovarian, glioblastoma, and AML not including acute promyelocytic leukemia, known to overexpress the WT1 protein who have progressive or recurrent measurable (may be measurable by tumor markers only, such as quantitative reverse transcriptase – polymerase chain reaction [RT-PCR] for WT1 transcript for AML, or cancer antigen 125 [CA-125] for ovarian carcinoma) neoplastic disease despite administration of standard therapy or for whom no standard of therapy exists are eligible for enrollment in this study. Patients must also be human leukocyte antigen (HLA)-A*0201+ and/or HLA-A*0206+; have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2; have adequate bone marrow and immune reserve and renal and hepatic function; and meet criteria for recovery from effects of previous antineoplastic therapies. Part 2: Adult patients with histologically or cytologically documented advanced stage glioblastoma or AML not including acute promyelocytic leukemia, known to overexpress the WT1 protein who have progressive or recurrent measurable (may be measurable by tumor markers only, such as quantitative RT-PCR for WT1 transcript for AML) neoplastic disease despite administration of standard therapy or for whom no standard of therapy exists are eligible for enrollment in this study. Patients must also be HLA-A*0201+ and/or HLA-A*0206+; have an ECOG Performance Status score of 0, 1, or 2; have adequate bone marrow and immune reserve and renal and hepatic function; and meet criteria for recovery from effects of previous antineoplastic therapies.
Investigational Product, Dosage, and Mode of Administration: Part 1: The following dose cohorts are planned: • 0.3, 0.9, 3.0 , and 9.0 mg WT2725 Dosing Emulsion All study drug will be administered by subcutaneous (sc) injection (at 2 anatomical sites) once every 7 days for 4 weeks, then once every 14 days for 6 weeks, and then once every 28 days until discontinuation. Part 2: The following dose cohorts are planned: • 18.0 and 27.0 mg WT2725 Dosing Emulsion All study drug will be administered by sc injection (at 2 anatomical sites) once every 7 days for 8 weeks, then once every 14 days for 10 weeks, and then once every 28 days until discontinuation.
Duration of Treatment: Patients may remain on study drug until evidence of confirmed progressive disease, intolerance to treatment with study drug, or fulfillment of any of the other criteria for discontinuation.
Reference Therapy, Dosage and Mode of Administration: Not applicable
Criteria for Evaluation: **Primary Endpoints:** The safety and tolerability of WT2725 Dosing Emulsion will be evaluated based on the occurrence of DLT and AEs, and the findings from clinical laboratory tests, vital signs measurements, body weight measurements, and electrocardiogram (ECG) results.

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The determination of the MTD of WT2725 Dosing Emulsion will be based on the incidence of DLT at each dose level and the overall safety profile of WT2725 Dosing Emulsion. The incidence of DLT will be evaluated during the DLT Evaluation Period, which extends from the day of the first dose to just prior to the fifth dose of study drug (Days 1 to 29). No more than 4 doses of study drug will be administered during the DLT Evaluation Period.

Dose-limiting toxicities are defined as any Grade 3 or greater AE that occurs after the administration of study drug during the DLT Evaluation Period that are not related to underlying disease, intercurrent illness, or concomitant medications (Changes in hematology parameters need to have been confirmed on repeat assessment and constitute at least a 2 grade shift. Grade 3 AEs of nausea, vomiting, and fatigue that are common and manageable in cancer patients will not be considered DLT if they can be ameliorated to < Grade 3 with standard supportive care management.). Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0.

Secondary Endpoints:

- Proportion of patients in each overall response category for each dose cohort based on irRC, modified IWG, and/or tumor markers, as appropriate, at each post-treatment tumor assessment and at the last assessment
- Percent change in tumor burden from baseline to each post-treatment tumor assessment and the last tumor assessment for each dose cohort
- The amount of immune response evaluated by:
    - measurement in peripheral blood of WT1 peptide-specific cytotoxic T lymphocyte (CTL) induction activity at each assessment time
    - measurement in peripheral blood of WT1 serum antibody titer at each assessment time
    - delayed-type hypersensitivity (DTH) to the WT2725 peptide at each assessment time
    - measurement of level of expression of CD8+, Foxp3, HLA class I, and WT1 protein in tumor tissue using immunohistochemistry (IHC) methods

Exploratory Endpoints:

- Correlation between the level of expression of WT1 protein and the degree of the immune response at each assessment time as measured by CTL induction
- Evaluation of changes in activity in peripheral blood mononuclear cells (PBMCs) after administration of study drug

Statistical Methods:

The Safety population will include all enrolled patients who receive at least 1 dose of study drug and will be used for the analysis of all safety and efficacy data except as noted. If needed, a DLT population will include all patients in the Safety population who are evaluable for DLT evaluation and will be used for analysis of DLT. If needed, an Efficacy population will include all patients in the Safety population who are evaluable for response and will be used for analysis of response.

Data will generally be summarized by enrolled or starting dose. Descriptive statistics including number of patients, mean, standard deviation, minimum, 25^{th} percentile, median, 75^{th} percentile, and maximum will be provided.

No imputation will be performed for missing data in this Phase 1 study.

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Safety measures will be summarized using descriptive statistics by enrolled dose cohort and listed for each patient. Adverse events also will be summarized by last dose administered before event start. **Sample Size Calculation:** The sample size is based on clinical and practical considerations for a Phase 1 dose escalation study using the rolling-six design, and is outside of statistical considerations.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation	Full Form
AE	Adverse experience/event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
CA-125	Cancer antigen 125
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
CV	Curricula vitae
DLT	Dose-limiting toxicity
DSWI	Diluting Solution for WT2725 Injection
DTH	Delayed-type hypersensitivity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of study
ePRO	Electronic patient reported outcomes
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage-colony stimulating factor
HIV	Human immunodeficiency virus

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation	Full Form
HLA	Human leukocyte antigen
ICH	International Conference on Harmonisation
Id	intradermal
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IND	Investigational New Drug
IPD	Important protocol deviation
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRC	Immune-related Response Criteria
IRB	Institutional Review Board
irSD	Immune-related stable disease
IWG	International Working Group response criteria in acute myeloid leukemia
LHRH	Luteinizing hormone-releasing hormone
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
PBMC	Peripheral blood mononuclear cell
PET	Positron-emission tomography
PPD-PVG	PPD Pharmacovigilance
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RP2D	Recommended phase 2 dose

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation	Full Form
RR	Respiration rate
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse experience/event
Sc	subcutaneous
SOC	System organ class
SPECT	Single-photon emission computed tomography
SPD	Sum of the products of the 2 largest perpendicular diameters
TAA	Tumor-associated antigen
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
W/O	Water-in-oil
WOPE	W/O pre-Emulsion
WT1	Wilms' tumor gene product 1

For the purposes of standardization, the following definitions will be used:

- Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to report to the sponsor for each study patient.
- Screened Patient: Any patient who signed the study specific informed consent and completed at least one study related procedure.
- Screen Failures: Any patient who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled.
- Study Drug (or study medication): Term to cover investigational drug.
- Enrolled Patient: Any patient who was successfully screened and enrolled into the Vaccine Induction Phase of the study.

4. INTRODUCTION

Cancer vaccines consisting of synthetic cancer antigen-derived peptides designed to elicit T cell immunity have been evaluated as a potential treatment for cancer in clinical trials for more than a decade. Although the success rate in inducing specific T-cell responses has been mixed, there have been reports of minor tumor regression and occasional objective responses.

Recent scientific advances have resulted in the identification of a large number of tumor-associated antigens (TAAs) and their epitopes recognized by human leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocytes (CTLs) from various types of malignant neoplasms (Buonaguro-2011). Cytotoxic T cells kill cancer cells by recognizing the major histocompatibility (MHC) class I-peptide complex on the surface of cancer cells. One such TAA is the Wilms' tumor gene product 1 (WT1), which was isolated as a gene responsible for Wilms' tumor, a pediatric renal cancer, and encodes a zinc finger transcription factor, which is involved in cell proliferation, differentiation, and apoptosis, and organ development. Expression of the wild-type WT1 gene has been found in various types of malignant tumors (Hutchings-2007) such as acute myeloid leukemia (AML), acute lymphoblastic leukemia, and myelodysplastic syndrome (MDS) at levels higher than those in normal bone marrow or peripheral blood and can confer oncogenic functions (Sugiyama-2005). In addition, various types of solid tumors, including breast, lung, thyroid, ovarian, glioblastoma, and colorectal, express the wild-type WT1 protein at higher levels than surrounding normal tissues (Nakatsuka-2006, Oji-2004).

Injection of peptides in aqueous solutions alone is generally not effective in stimulating CTL response. Therefore, adjuvants, such as water-in-oil (W/O) emulsion, have been used to enhance the immunogenicity of TAAs by creating a depot effect that prevents access of the immunogen to tissue and blood-borne proteases, while facilitating TAAs translocation into antigen-presenting cells.

The WT2725 drug product is referred to as WT2725 Dosing Emulsion and consists of WT2725, the acetate salt of a synthetic peptide with the same sequence as the naturally occurring peptide $WT1_{126\text{-}134}$, diluted in a peptide diluting solution, and administered with a novel adjuvant (W/O pre-Emulsion). WT2725 administered intradermally (id) or subcutaneously (sc), is thought to be presented on the surface of antigen-presenting cells, eg, dendritic cells, as an MHC class I-peptide complex to be recognized by T cells. As a consequence, vaccination with WT2725 Dosing Emulsion may stimulate the host immune system to induce a CTL response against cancer cells that overexpress the WT1 protein, resulting in cell lysis and inhibition of cancer cell proliferation.

Nonclinical in vitro pharmacology studies confirmed that the WT2725 peptide bound to the human antigen-presenting molecule, HLA-A*0201, and induced CD8+ T cells reactive to the $WT1_{126\text{-}134}$ peptide in human peripheral blood mononuclear cells (PBMCs) from an HLA-A*0201+ healthy donor. Nonclinical in vivo pharmacology studies confirmed that WT2725 Injection mixed with the novel W/O pre-Emulsion induced HLA-A*0201-restricted and WT2725 peptide-specific CTLs in HLA-A*0201-expressing transgenic mice.

Additionally, when the WT2725 peptide sequence was analyzed using a web server for the prediction of human MHC class I-peptide binding, the binding affinity to HLA-A*0206 was strong therefore suggesting that WT2725 is expected to bind to not only HLA-A*0201 but also

HLA-A*0206. HLA-A*0206-restricted and $WT1_{126-134}$-reactive CTLs were induced using HLA-A*0206+ PBMCs and the induced CTLs showed killing activity to a target cell line transfected with HLA-A*0206 and endogenously expressing WT1 protein (International Application Published under the Patent Cooperation Treaty: WO2009/072610). It is reported that valine and glutamine at position 2 in peptides are anchor residues of HLA-A*0206 (Sudo-1995) and that valine and leucine at position 9 are anchor residues of HLA-A*0206. The WT2725 peptide has an anchor residue of HLA-A*0206 at position 9. Several HLA-A*0201 binding peptides which have an anchor residue of HLA-A*0206 at position 9 are reported to be presented by HLA-A*0206 or to elicit a CTL response with restriction of HLA-A*0206 (Eifuku-2001, Fleischhauer-1996, Li-2008, Zhang-2003).

In repeat-dose toxicity studies of up to 13-weeks duration in cynomolgus monkeys, id or sc injection of the planned clinical WT2725 Dosing Emulsion was associated with macroscopic and microscopic findings along with clinical observations at the injection site. Additionally, non-adverse macroscopic and microscopic findings were observed at the injection site following id or sc administration of the Control dosing emulsion. The skin reactions observed following administration of WT2725 Dosing Emulsion were the dose-limiting toxicity (DLT) in these studies, were noted to be reversible, and are readily monitorable with regular observation of the injection site.

In a bacterial reverse gene mutation (Ames) assay and an in vitro chromosomal aberration assay, WT2725 did not induce mutations or chromosomal aberrations.

In vitro studies demonstrated that WT2725 was unstable in human and monkey blood, and WT2725 was not detected in monkey plasma at any time point after a single id or sc administration.

In previous clinical studies of the $WT1_{126-134}$ peptide (administered with various adjuvants and combination therapy), few significant adverse reactions were noted, however various local skin reactions were observed (Kaida-2011, Keilholz-2009, Kuball-2011, Rezvani-2008, Gentilini-2006, Soeda-2010).

Rezvani et al (2008) reported that $WT1_{126-134}$ peptide in combination with $PR1_{169-177}$ peptide using Montanide ISA-51 VG adjuvant and granulocyte macrophage-colony stimulating factor (GM-CSF) resulted in induction of WT1-specific CD8+ T cells. Additionally, Maslak et al (2010) using a vaccine of multiple WT1 peptides reported WT1-specific T-cell responses in the majority of patients and significant increases in interferon (IFN)-γ-secreting cells and frequency of WT1 tetramer+ CD8+ T cells in patients who were HLA-A*0201+.

This first clinical study of WT2725 Dosing Emulsion is an open-label, dose escalation design to evaluate the safety and tolerability of WT2725 Dosing Emulsion delivered via sc injection in order to define the maximum tolerated dose (MTD). Additionally, antitumor activity and biomarkers indicative of immune response will be evaluated. WT2725 Dosing Emulsion will be administered as monotherapy to patients with one of the following advanced malignancies: non-small cell lung, ovarian, glioblastoma, and AML (not including acute promyelocytic leukemia), known to overexpress the WT1 protein. Tumors that do not overexpress the WT1 protein will not be sensitive to WT1-specific CTLs therefore a subset of malignancies that do overexpress the WT1 protein was selected based on a review of the literature (Franko-2010, Nakatsuka-2006, Oji-2003). A rolling-six design (Skolnik-2008) will be used for enrollment into

ascending dose cohorts to determine the MTD. Patients may remain on study drug until there is evidence of confirmed progressive disease, intolerance to treatment with study drug, or fulfillment of any of the other criteria for discontinuation.

4.1. Study Rationale

Parenteral administration of the WT2725 peptide results in detection and presentation on the surface of antigen presenting cells, eg, dendritic cells, as an MHC class I-peptide complex to be recognized by T cells. As a result, vaccination with WT2725 Dosing Emulsion may stimulate the host immune system to induce a CTL response against WT1-expressing cells, resulting in cell lysis and inhibition of cancer cell proliferation.

Treatment with other WT1 peptide vaccines in clinical trials has shown evidence of immunogenicity and clinical response in various malignancies. Based on the nonclinical findings for WT2725 and the reported clinical results with other WT1 peptide vaccines in cancer patients there is an expectation that some clinical benefit may be derived from treatment with WT2725 Dosing Emulsion. In these other clinical trials, as well as in the nonclinical studies of WT2725, there have been limited significant adverse effects other than local injection site skin reactions.

This study will assist with determining which doses level(s) to use in future clinical studies. In addition, this study will evaluate both clinical and immunological response.

4.2. Dose Justification

4.2.1. Starting Dose Level

Two repeat-dose toxicology studies of up to 13-weeks duration conducted in cynomolgus monkeys using the planned clinical WT2725 Dosing Emulsion administered id (1.0 and 3.0 mg/body) and sc (3.0 and 9.0 mg/body) once a week were conducted. In both studies, WT2725 Dosing Emulsion was associated with macroscopic and microscopic findings along with clinical observations at the injection site. Clinical observations at the injection site consisted of swelling, erythema, and/or crust which, in some cases, progressed to ulceration and erosion. These skin reactions were the DLT as persistence of ulceration/erosion for up to 5 days led to early euthanasia in some animals and discontinuation of dosing in the high dose groups after the tenth or eleventh administration in females and males, respectively. In surviving animals, the skin reactions at the injection site were noted to be reversible with discontinuation of dosing and administration of topical or intramuscular antibiotics. Systemic toxicological findings were limited to intermittent decreases in body weight and alterations in hematology and blood chemistry parameters that were judged to be secondary to stress and inflammatory changes at the injection site.

A clinical study of a HLA-A*02-restricted $WT1_{126-134}$ peptide vaccine, in which a peptide with the same sequence as the WT2725 peptide was administered with the Montanide ISA-51VG adjuvant, reported administration of 1.0 and 3.0 mg dose levels without apparent DLT (Kaida-2011). Vaccine (0.1 mL) was injected id into 6 sites (bilateral arms, 2 sites on the lower abdomen, and femoral areas) biweekly on Days 8 and 22. Gemcitabine was administered concurrently on Days 1, 8, and 15. Although the scheduled study period was 2 courses, treatment was continued at the patient's request if there was no disease progression or serious adverse events (SAEs). Grade 1 or 2 skin reaction at the site of vaccination, characterized by redness,

pruritus, and induration, was observed in all patients (n = 25). WT1-specific T cells in peptide-stimulated culture were detected by tetramer assay in 46% (5 of 11) of patients.

The results of this clinical trial provide information about the safety of the $WT1_{126-134}$ peptide vaccine based on pharmacological action of $WT1_{126-134}$ peptide specific CTL. Although the adjuvant used in the clinical trial was different from that of the WT2725 Dosing Emulsion in its composition, the potential to induce $WT1_{126-134}$ peptide specific CTL with the Montanide ISA-51VG adjuvant and the novel W/O pre-Emulsion for WT2725 Dosing Emulsion was evaluated and found to be similar in HLA-A02 transgenic mice. Furthermore, the W/O pre-Emulsion to be used with WT2725 by itself caused no severe skin lesion or systemic toxicity in the 13-week cynomolgus monkey studies. In addition, the same W/O pre-Emulsion has already been administered to several patients in 2 ongoing clinical trials of another modified peptide from the HLA-A*2402-restricted $WT1_{235-243}$ peptide in Japan. In the Phase 1 solid tumor trial, as of 31 Dec 2011, for 3 enrolled patients only Grade 1 adverse events (AEs) had been reported including injection site reactions and for 1 additional patient Grade 2 injection site reaction and hypertension had been reported; this is preliminary draft data from an active, unlocked database and subject to change (data on file Chugai Pharmaceutical Co., Ltd). In the Phase 1/2 MDS study, as of the same date, for the one enrolled patient no injection site reactions had been observed, although Grade 4 neutropenia and thrombocytopenia, Grade 3 febrile neutropenia and leucopenia, and Grade 2 urticaria had been reported in addition to other Grade 1 AEs; this is preliminary draft data from an active, unlocked database and subject to change (data on file Sumitomo Dainippon Pharma Co., Ltd). Because low blood cell counts are common with MDS and there have been few other toxicities greater than Grade 1 in these trials, the novel W/O pre-Emulsion used with WT2725 is not expected to cause unexpected severe AEs.

In terms of clinical efficacy, it has been reported that sc injections of 0.2 mg $WT1_{126-134}$ peptide in combination with 0.5 mg $PR1_{169-177}$ peptide using Montanide ISA-51VG adjuvant and GM-CSF resulted in induction of WT1-specific CD8+ T cells (Rezvani-2008). The dose of 0.2 mg per peptide also has been reported to be within the range found to be safe and active for other peptide vaccines (Maslak-2010). These reports suggest that this dose level may have a likelihood of immunological activity.

For this study, a clinical starting dose of 0.3 mg/body (2 injection sites) is planned for Part 1, based on the following considerations:

1. 0.3 mg/body by sc administration is equivalent to 1/10th the lower dose (3.0 mg/body WT2725 Dosing Emulsion) in the sc cynomolgus monkey study at which a severe skin lesion (ulceration) was noted in one animal. Of note, similar lesions observed at the highest dose (9.0 mg/body) showed reversibility with discontinuation of dosing and antibiotic treatment. In addition, skin lesions observed in the 1.0 mg/body id cohort showed reversibility without discontinuation of dosing or antibiotic treatment.
2. Similar skin lesions have been observed in clinical studies of $WT1_{126-134}$ peptide (doses ranging from 0.2 mg – 3 mg) (Kaida-2011, Keilholz-2009, Kuball-2011, Rezvani-2008, Gentilini-2006, Soeda-2010). Treatment for these skin lesions has included dermal steroid treatment and topical nonsteroidal anti-inflammatory drugs.
3. There were no DLTs reported from the published clinical studies of the naturally occurring $WT1_{126-134}$ peptide. A dose of 0.3 mg/body is approximately 1/10th the dose of

$WT1_{126-134}$ peptide already used clinically, albeit with a different adjuvant, different administration route, and different number of injection sites.

4. As it is ethically important to select a starting dose at which some clinical benefit for cancer patients may be expected, based on the results of clinical studies of other WT1 peptides 0.3 mg/body is anticipated to be within an immunologically active dose range.

4.2.2. Additional Dose Levels for Part 2

Initial dose escalation in this study was completed, with the highest planned dose of 9.0 mg being administered without dose-limiting toxicity. This dose was considered the recommended phase 2 dose (RP2D), and additional patients were enrolled and initiated treatment at this dose. As of May 2014 the most common drug-related adverse reactions reported with doses up to 9.0 mg were low grade localized injection site reactions with itching, erythema, pain, bruising, and/or swelling. A total of 14 treatment emergent serious adverse events (SAEs) were reported in 9 patients; there was no pattern in the types of treatment emergent SAEs reported. Two serious adverse reactions (SARs; defined as SAEs that were assessed as at least possibly related to study drug) were reported in 2 patients; tumor necrosis was reported in 1 patient, and rash maculo-papular was reported in 1 patient. Further with the expanded cohorts of patients treated at 9.0 mg, no important unanticipated risks, potential risks, or safety signals have been observed, the 9.0 mg dose is not considered the MTD. Preliminary review of efficacy data indicates that WT2725 Dosing Emulsion has the potential to be of benefit to patients, which may be further enhanced by more regular injections in the early stages of treatment. Based on the results from these initial patients in Part 1, additional dose escalation, at no more than double the prior dose level, is being explored to evaluate safety, tolerability, and efficacy. In addition, extension of the induction and consolidation phases of treatment will be explored.

4.2.3. Route of Administration

Langerhans cells, which function as antigen-presenting cells, are widely distributed within the epidermis, and there are multiple reports of id and sc dosing of cancer vaccines to sequester antigen in the intradermal or subcutaneous tissue near the epidermis to ensure efficient recognition. A previous clinical study using $WT1_{235-243,\ 2M\rightarrow Y}$ peptide (Oka-2008, Oka-2004) demonstrated that there was induction of WT1-specific CTL as a result of id dosing. A study by Keilholz et al (2009) of $WT1_{126-134}$ peptide in keyhole-limpet-hemocyanin adjuvant plus GM-CSF demonstrated induction of WT1-specific CTL following id and sc injection and Rezvani et al (2008) using deep sc injection of $WT1_{126-134}$ peptide in combination with $PR1_{169-177}$ peptide using a different adjuvant observed induction of WT1-specific CD8+ T cells following sc injection of the 2 peptides. Subcutaneous dosing may have several advantages over id dosing including less injection site pain for patients and easier administration.

4.2.4. Dosing Interval

Cancer vaccines generally have a slow onset of efficacy, and efficacy requires a significant amount of CTL induction in accord with the amount of disease in advanced malignancies. The optimal dosing interval for cancer vaccine treatments is unknown. Based on preceding peptide vaccine clinical trials, 1 week is thought to be an appropriate initial dosing interval for a Phase 1 trial.

4.3. Summary of Known Potential Risks and Benefits

Treatment with other WT1 peptide vaccines, including some with the same sequence as the WT2725 peptide, in clinical trials has shown evidence of immunogenicity and clinical response in various malignancies. Based on the nonclinical findings for WT2725 and the reported clinical results with other WT1 peptide vaccines in cancer patients there is an expectation that some clinical benefit may be derived from treatment with WT2725 Dosing Emulsion. In these clinical trials, as well as in the nonclinical studies of WT2725, there have been a limited number of significant adverse reactions other than local injection site skin reactions therefore presenting an acceptable benefit/risk profile to study participants.

In this study at doses up to the RP2D of 9.0 mg, as of May 2014 the most common drug-related adverse reactions reported were low grade localized injection site reactions with itching, erythema, pain, bruising, and/or swelling. A total of 14 treatment-emergent SAEs were reported in 9 patients; there was no pattern in the types of treatment emergent SAEs reported. Two SARs were reported in 2 patients; tumor necrosis was reported in 1 patient, and rash maculo-papular was reported in 1 patient. Further with the expanded RP2D patients, no important unanticipated risks, potential risks, or safety signals have been observed, the 9.0 mg dose is not considered the MTD. Preliminary review of efficacy data indicates that WT2725 Dosing Emulsion has the potential to be of benefit to patients, which may be further enhanced by more regular injections in the early stages of treatment. Based on the results from these initial patients in Part 1, additional dose escalation, at no more than double the prior dose level, is being explored to evaluate safety, tolerability, and efficacy. In addition, extension of the induction and consolidation phases of treatment will be explored.

5. STUDY OBJECTIVES

5.1. Primary Objectives

The primary objectives are:

- to evaluate the safety and tolerability of WT2725 Dosing Emulsion
- to determine the MTD of WT2725 Dosing Emulsion based on the evaluation of DLT.

5.2. Secondary Objectives

The secondary objectives are:

- to describe antitumor responses to WT2725 Dosing Emulsion based on the irRC (Wolchok-2009, Hoos-2010), modified International Working Group response criteria in acute myeloid leukemia (IWG) (Cheson-2003), and/or tumor markers
- to evaluate the immune response to WT2725 Dosing Emulsion based on a series of circulating biomarkers in peripheral blood, delayed-type hypersensitivity (DTH) to the WT2725 peptide, and immunohistochemistry in tumor tissue.

5.3. Other Objectives

The other objectives are:

- to evaluate immune response by level of WT1 protein expression in tumor cells
- to obtain blood serum for future retrospective analyses of additional biomarkers.

6. STUDY ENDPOINTS

6.1. Primary Endpoints

The safety and tolerability of WT2725 Dosing Emulsion will be evaluated based on the occurrence of DLT and AEs, and the findings from clinical laboratory tests, vital signs measurements, body weight measurements, and electrocardiogram (ECG) results.

The determination of the MTD of WT2725 Dosing Emulsion will be based on the incidence of DLT at each dose level and the overall safety profile of WT2725 Dosing Emulsion. The incidence of DLT will be evaluated during the DLT Evaluation Period, which extends from the day of the first dose to just prior to the fifth dose of study drug (Days 1 to 29). No more than 4 doses of study drug will be administered during the DLT Evaluation Period.

Dose-limiting toxicities are defined as any Grade 3 or greater AE that occurs after the administration of study drug during the DLT Evaluation Period that are not related to underlying disease, intercurrent illness, or concomitant medications (Changes in hematology parameters need to have been confirmed on repeat assessment and constitute at least a 2 grade shift. Grade 3 AEs of nausea, vomiting, and fatigue that are common and manageable in cancer patients will not be considered DLT if they can be ameliorated to < Grade 3 with standard supportive care management.). Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 (NCI-2009).

6.2. Secondary Endpoints

- Proportion of patients in each overall response category for each dose cohort based on irRC, modified IWG, and/or tumor markers, as appropriate, at each post-treatment tumor assessment and at the last assessment
- Percent change in tumor burden from baseline to each post-treatment tumor assessment and the last tumor assessment for each dose cohort
- The amount of immune response evaluated by:
    - measurement in peripheral blood of WT1 peptide-specific CTL induction activity at each assessment time
    - measurement in peripheral blood of WT1 serum antibody titer at each assessment time
    - DTH to the WT2725 peptide at each assessment time
    - measurement of level of expression of CD8+, Foxp3, HLA class I, and WT1 protein in tumor tissue using immunohistochemistry (IHC) methods

6.3. Exploratory Endpoints

- Correlation between the level of expression of WT1 protein and the degree of the immune response at each assessment time as measured by CTL induction
- Evaluation of changes in activity in peripheral blood mononuclear cells (PBMCs) after administration of study drug

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 1, open-label, dose-escalation, 2-part study in adult patients with advanced malignancies known to overexpress the WT1 protein and who have progressive or recurrent measurable (may be measurable by tumor markers only, such as quantitative reverse transcriptase – polymerase chain reaction [RT-PCR] for WT1 transcript for AML, or cancer antigen 125 [CA-125] for ovarian carcinoma) neoplastic disease despite administration of standard therapy or for whom no standard of therapy exists. In Part 1 of the study patients with one of the following malignancies: non-small cell lung, ovarian, glioblastoma, and acute myeloid leukemia (AML; not including acute promyelocytic leukemia) meeting the above criteria are eligible. In Part 2 of the study patients with glioblastoma and AML (not including acute promyelocytic leukemia) meeting the above criteria are eligible.

Both parts of the study will primarily evaluate DLT and define the MTD of WT2725 Dosing Emulsion during the DLT Evaluation Period, which extends from the day of the first dose of study drug to just prior to the fifth dose (Days 1 - 29). Dose-limiting toxicities are defined as any Grade 3 or greater AE that occurs after the administration of study drug during the DLT Evaluation Period that are not related to underlying disease, intercurrent illness, or concomitant medications (Changes in hematology parameters need to have been confirmed on repeat assessment and constitute at least a 2 grade shift. Grade 3 AEs of nausea, vomiting, and fatigue that are common and manageable in cancer patients will not be considered DLT if they can be ameliorated to < Grade 3 with standard supportive care management.). In addition, antitumor activity and biomarkers indicative of immune response will be evaluated from the first dose until discontinuation of the patient from the study. An end of study assessment will take place within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy.

The initial patients in each dose escalation cohort will be enrolled at least one week apart to evaluate initial safety from the first 2 patients, then a “rolling-six” design will be employed that allows accrual of 2 to 6 patients concurrently in each dose escalation cohort. This design was chosen in an effort to reduce the delays associated with patient accrual using the classical “3 + 3” design as severe immediate reactions are not anticipated following administration of WT2725 Dosing Emulsion. The decision to enroll an additional patient in the current dose cohort, to dose escalate to the next dose cohort, or to dose de-escalate to a lower dose cohort can be made without having to suspend enrollment following the initial enrollment of 3 patients, as in the “3 + 3” design. The decision regarding dose cohort for an incoming patient is dependent on the number of DLTs that have been observed, the number of patients enrolled at any time and the duration of their enrollment, and in Part 2 of the study the malignancy type. The goal remains to define the MTD as the dose level where no more than 1 of 6 patients experiences a DLT when 2 of 2 to 6 patients experiences a DLT at the next higher dose level. Meetings to review study execution and enrollment/dosing decisions will be held at least monthly between the sponsor, clinical sites, and the medical monitor. The expected time to enroll each dose escalation cohort (2 – 6 patients) is between 6 and 12 weeks.

The following dose cohorts of WT2725 Dosing Emulsion are planned for Part 1 of the study:

- 0.3, 0.9, 3.0, and 9.0 mg

An approximate 3-fold increase in dose between cohorts (eg, 0.3, 0.9, 3.0 mg) will allow this dose range to be explored with the fewest number of dose levels.

The following dose cohorts of WT2725 Dosing Emulsion are planned for Part 2 of the study:

- 18.0 and 27.0 mg

No more than a 2-fold increase in dose between cohorts (eg, 9.0, 18.0, 27.0 mg) will allow this higher dose range to be explored more conservatively.

In Part 1 of the study, the 0.3 mg cohort will be conducted first. After safety and tolerability have been established for the first dose cohort, enrollment of subsequent patients will be conducted sequentially in subsequent cohorts and continue until the MTD or all planned cohorts are attained. Enrollment of each cohort may include patients with any of the eligible tumor types. Enrollment of the highest tolerable dose cohort (MTD or highest planned cohort) will continue until there are at least 6 patients total in the study with each tumor type that are evaluable for DLT, biomarkers, and response. This dose is considered the recommended phase 2 dose (RP2D). Enrollment of up to 3 RP2D cohorts of 10 patients each of specific tumor types may take place at this dose in order to further characterize the safety and efficacy of WT2725 Dosing Emulsion at this dose in these subsets of patients.

Additional dose escalation cohorts after the initial expansion cohorts may be enrolled if a MTD has not been determined and significant signs of toxicity have not been observed in the expansion cohorts.

In Part 2 of the study, the 18.0 mg cohort will be conducted first. After safety and tolerability have been established for the 18.0 mg cohort, enrollment of subsequent patients will be conducted sequentially in the 27.0 mg cohort. Approximately 10 patients at each dose level (18.0 and 27.0 mg) with at least 4 patients with each malignancy type (glioblastoma and AML) will be enrolled at each of these dose levels. If the MTD is reached in Part 2 before the total of 20 patients are enrolled, remaining patients will be enrolled at the prior dose level. Patients who experience DLT may remain on the study at a reduced dose if they are deriving some therapeutic benefit from study drug and fulfill the criteria for study continuation for subsequent dosing (see Section 8.3.2); these decisions will be addressed on a case by case basis. Patients who experience a DLT or other significant toxicity at this reduced dose will be discontinued from receiving further study drug. In the event that a dose level is excluded from further study due to dose limiting toxicity all patients may continue the study at the most recently completed dose without DLT, eg, if the 27.0 mg dose is excluded due to DLT all patients may continue at 18.0 mg.

After the DLT Evaluation Period, if a patient experiences a study drug-related Grade 3 toxicity, there will be a review of safety data to determine appropriate dosing for that patient and other patients on study, as well as for any subsequently enrolled patients.

In the event that a Grade 4 or greater toxicity is reported at any time during the study, the sponsor and the investigator will conduct a thorough evaluation of the available safety data to decide whether to continue enrolling new patients into the study.

Patients who have completed the consolidation phase of their assigned cohort and have not experienced a DLT, ≥ Grade 2 study drug-related injection-site reaction, or required a dose

reduction may have their dose level escalated to that of the highest cohort for which safety and tolerability have been established. Patients may remain on study drug until evidence of confirmed progressive disease, intolerance to study drug, or fulfillment of any of the other criteria for discontinuation (see Section 12.2).

Each part of the study will include 3 treatment phases based on intended timing of study drug dosing as indicated below:

Part 1:

- Vaccine Induction Phase: once every 7 days for 4 weeks (doses 1 - 5)
- Consolidation Phase: once every 14 days for 6 weeks (doses 6 - 9)
- Maintenance Phase: once every 28 days until discontinuation (dose 10 and thereafter)

Part 2:

- Vaccine Induction Phase: once every 7 days for 8 weeks (doses 1 - 9)
- Consolidation Phase: once every 14 days for 10 weeks (doses 10 – 15 [maximum 6 doses])
- Maintenance Phase: once every 28 days until discontinuation (dose 16 and thereafter)

Approximately 60 to 80 patients total including replacements will be dosed in this clinical trial. The total number of patients dosed in this clinical trial will be determined by the number of patients treated in each dose cohort and the number of dose cohorts necessary to determine the MTD, as well as the number of RP2D cohorts enrolled. If all 4 dose escalation cohorts are necessary in Part 1, and if 6 enrolled patients are required in each dose escalation cohort and/or tumor type, then 24 patients evaluable for DLT, biomarkers, and response would be necessary in the Part 1 dose escalation. In addition, up to 30 patients may be enrolled in the RP2D cohorts in Part 1. If both dose escalation cohorts are necessary in Part 2, and if 10 patients are enrolled in each of these cohorts, then 20 patients will be enrolled in Part 2. Patients who discontinue from the study prior to completion of the DLT, biomarker response evaluation period will be replaced likely increasing the total number of patients enrolled.

Four to 8 investigative sites in the United States (US) will be utilized to enroll patients in Part 1 of the study. An additional 2 sites in the US may be opened to enroll patients in Part 2.

A study schematic is presented in Figure 1 for Part 1 and in Figure 2 for Part 2. Details of study assessments and other procedures to be performed at each visit in Part 1 are presented in Table 3, Schedule of Assessments for Screening and Vaccine Induction Phase – Part 1 and Table 4, Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study – Part 1; and Section 11, Treatment Plan. Details of study assessments and other procedures to be performed at each visit in Part 2 are presented in Table 5, Schedule of Assessments for Screening and Vaccine Induction Phase – Part 2 and Table 6, Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study – Part 2; and Section 11, Treatment Plan.

Figure 1: Study Schematic – Part 1

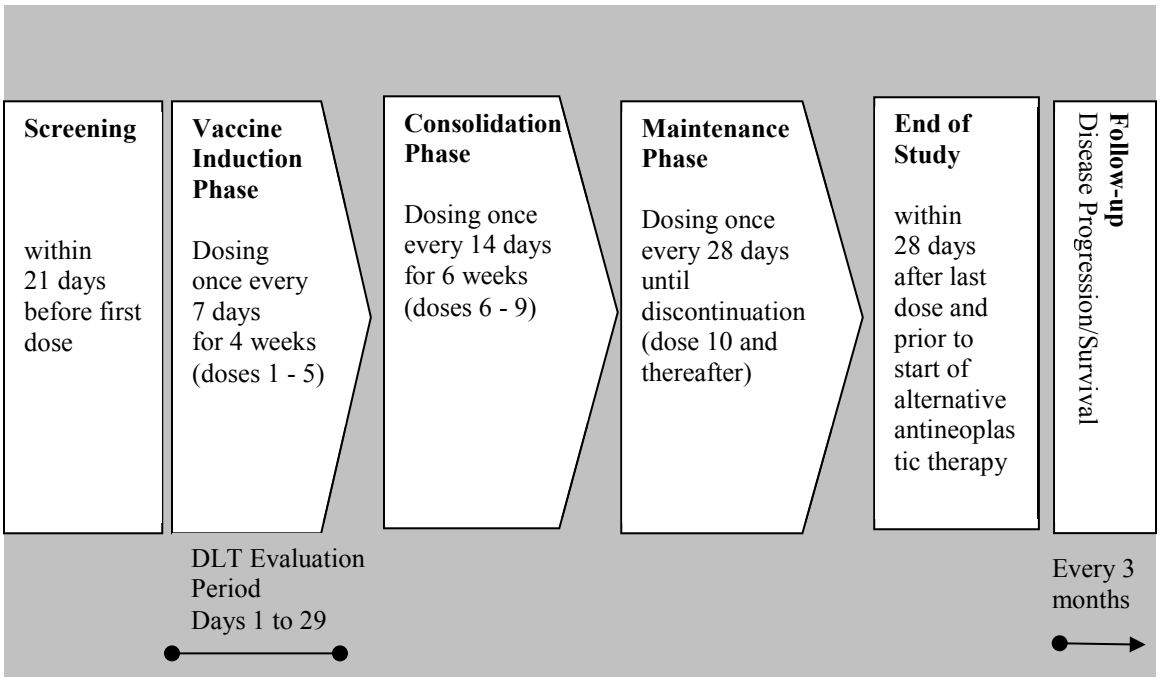


Figure 2: Study Schematic – Part 2

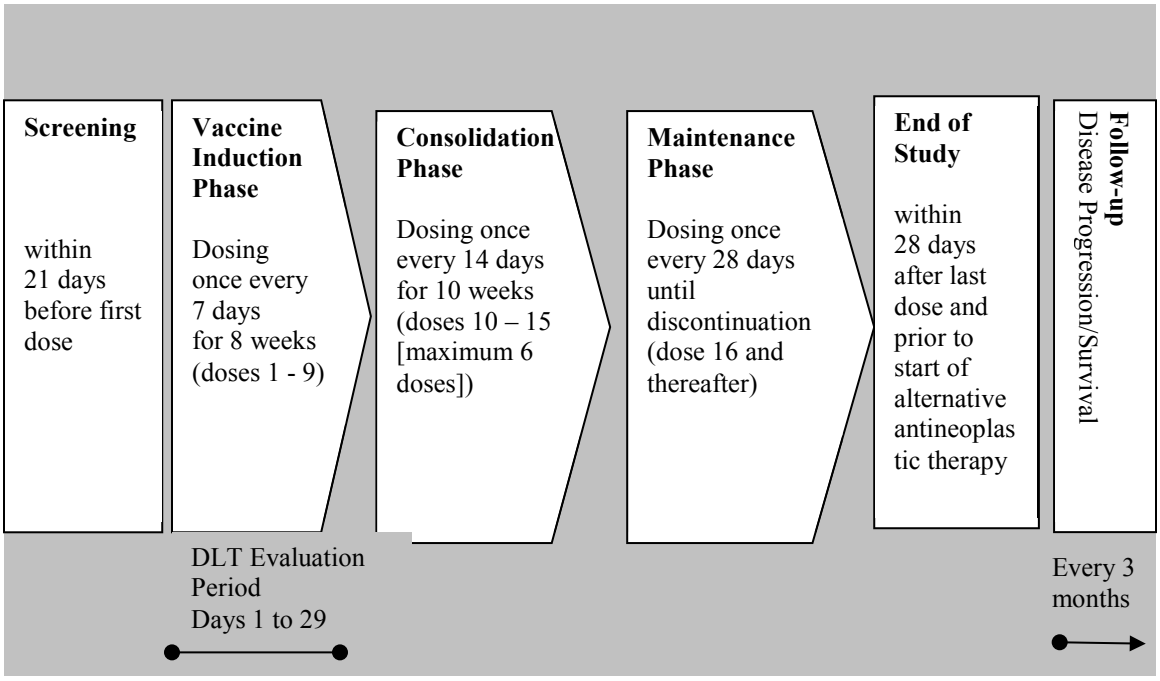


Table 3: Schedule of Assessments for Screening and Vaccine Induction Phase – Part 1

	Screening		Vaccine Induction Phase[a,b]								
	within 14/21 days before 1st dose (-1 – -14/-21)	within 7 days before 1st dose (-1 - -7)		1st dose		2nd dose	3rd dose	4th dose		5th dose	
			Day -2	Day 1 (-1)	Day 3	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 27	Day 29 (-1)	Day 31
Informed consent	X										
Inclusion/exclusion	X	X									
Continuation criteria				X[c]		X[c]	X[c]	X[c]		X[c]	
Study drug administration				X		X	X	X		X	
Medical history	X										
Physical exam		X		X[c]		X[c]	X[c]	X[c]		X[c]	
Height		X									
Weight		X		X[c]		X[c]	X[c]	X[c]		X[c]	
Vital Signs[d]		X		X[c]		X[c]	X[c]	X[c]		X[c]	
ECOG performance status		X		X[c]		X[c]	X[c]	X[c]		X[c]	
HLA typing[e]	X										
Serum pregnancy test[f]	X			X[c]							
Serology[g]	X										
Hematology/ serum chemistry[h]		X		X[c,i]		X[c]	X[c]	X[c]		X[c]	
Urinalysis		X		X[c,i]			X[c]			X[c]	
12-lead ECG		X		X[c,i]						X[c]	
DTH skin test injection			X[j]	X[j,k]					X[j]	X[j,k]	

Table 3: Schedule of Assessments for Screening and Vaccine Induction Phase – Part 1 (Continued)

	Screening		Vaccine Induction Phase[a,b]								
	within 14/21 days before 1st dose (-1 – -14/-21)	within 7 days before 1st dose (-1 - -7)	Day -2	1st dose Day 1 (-1)	Day 3	2nd dose Day 8 (-1)	3rd dose Day 15 (-1)	4th dose Day 22 (-1)	Day 27	5th dose Day 29 (-1)	Day 31
DTH skin test evaluation[l]				X[m]	X[n]					X[m]	X[n]
Blood sample for CTL		X		X[c]		X[c]	X[c]	X[c]		X[c]	
Blood sample for Anti-WT1 antibody				X[c]			X[c]			X[c]	
Blood sample for PBMC isolation				X[c]						X[c]	
Blood sample for retrospective biomarker analyses				X[c,o]	X[o]	X[c]	X[c]			X[c]	
IHC tumor samples		X[p,q]									
Tumor assessment	X[r]									X[s]	
Adverse events	→										
Concomitant medications	→										

Abbreviations: AML = acute myeloid leukemia, CA-125 = cancer antigen 125, CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, FSH = follicle-stimulating hormone, HLA = human leukocyte antigen, IHC = immunohistochemistry, irRC = immune-related response criteria, IWG = International Working Group response criteria in acute myeloid leukemia, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PET = positron-emission tomography, RT-PCR = reverse transcriptase-polymerase chain reaction, SPECT = single-photon emission computed tomography, WT1 = Wilms' tumor gene product 1

[a] Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.1).

[b] All patients should complete an End of Study visit (see Table 4) within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy.

Footnotes continued on the next page.

[c] Prior to study drug administration.
[d] Includes systolic and diastolic blood pressures, pulse, respirations rate, and oral body temperature.
[e] If HLA typing has been performed previously, these results may be used, otherwise HLA typing should be the first procedure performed during screening.
[f] For females of child-bearing potential.
[g] Includes hepatitis B and C, human immunodeficiency virus (HIV)-1, and HIV-2, if there are signs or symptoms suggestive of infection.
[h] See Section 22 (Appendix IV) for list of required laboratory tests at each visit.
[i] Assessment may be omitted if an assessment was performed within the previous 3 days. If there are multiple assessments the most recent ones should be used.
[j] Perform DTH skin test injections approximately 48 hours (but no sooner than 24 hours) prior to the evaluation.
[k] Perform DTH skin test injections immediately before administration of study drug.
[l] If the DTH reactivity results in erythema with induration greater than 2 cm, or leads to ulceration of the skin test site, further DTH testing should not be conducted for the patient.
[m] Evaluation should be made on the planned dosing day, prior to study drug administration.
[n] Evaluation should be approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injection.
[o] Samples obtained 6 hours (± 30 minutes) and 48 hours (± 6 hours) postdose.
[p] In place of tumor tissue samples from a biopsy during screening, archived tumor tissue samples may be provided. Availability of tumor tissue samples should be determined during screening through provision of the accession number or other identification number. If necessary, the tumor tissue sample biopsy should be performed after study eligibility has been confirmed and before the first dose of study drug. The tumor tissue samples will only be provided to the sponsor for patients who receive study drug. In place of archival tumor tissue samples, patients with AML should have available a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. Patients with AML should also have peripheral blood assessed for blasts and WT1 transcript.
[q] IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.
[r] Tumor assessments (per irRC for solid tumors, modified IWG for AML, and/or standard tumor markers as appropriate eg, CA-125 for ovarian carcinoma and quantitative RT-PCR for WT1 transcript for AML) are not required to be repeated if they have been performed within the 28 days before first dose (there are no variations allowed beyond this window). If multiple assessments are available, the most recent ones should be used as the baseline result. Data from at least one additional historical assessment prior to the baseline assessment should also be provided, if available. Progressive disease requires confirmation by a repeat, consecutive assessment at least 4 weeks after the date of first documentation, unless rapid clinical deterioration is seen. For patients with glioblastoma, progressive disease should additionally be confirmed by SPECT, perfusion MRI, MRI spectroscopy or C-14 methionine PET or pathology from available surgical/biopsy specimens to differentiate from pseudoprogression. For patients with ovarian cancer that express CA-125, progressive disease should additionally be confirmed by CA-125 (≥ 2x higher of ULN or on study nadir). For patients with AML, bone marrow aspirations/biopsies are to be provided at baseline and subsequently when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at baseline and at least every 4 weeks or more frequently as clinically indicated.
[s] Tumor markers drawn from peripheral blood samples should be assessed at least every 4 weeks after the 1st dose but may be performed more frequently (For other tumor assessments, perform every 8 weeks after 1st dose or more frequently as clinically indicated).

Table 4: Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study – Part 1

	Consolidation Phase[a,b]						**Maintenance Phase[a,b]**	**End of Study[b]**		**Follow-up**
	6th dose	**7th dose**	**8th dose**		**9th dose**					
	Day 43 (±2)	**Day 57 (±2)**	**Day 71 (±2)**	**Day 83**	**Day 85 (±2)**	**Day 87**	**every 28 (+7) days**	**48 hours before End of Study Visit**	**within 28 days after last dose**	**every 3 months**
Continuation criteria	X[c]	X[c]	X[c]		X[c]		X[c]			
Study drug administration	X	X	X		X		X			
Physical exam	X[c]	X[c]	X[c]		X[c]		X[c]		X	
Weight	X[c]	X[c]	X[c]		X[c]		X[c]		X	
Vital Signs[d]	X[c]	X[c]	X[c]		X[c]		X[c]		X	
ECOG performance status	X[c]	X[c]	X[c]		X[c]		X[c]		X	
Serum pregnancy test[e]									X	
Hematology/ serum chemistry[f]	X[c]	X[c]	X[c]		X[c]		X[c]		X	
Urinalysis	X[c]	X[c]	X[c]		X[c]		X[c]		X	
12-lead ECG		X[c]			X[c]		X[c]		X	
DTH skin test injection				X[g]	X[g,h]			X[g]		
DTH skin test evaluation					X[i]	X[j]			X[j]	
Blood sample for CTL	X[c]	X[c]	X[c]		X[c]		X[c]		X	
Blood sample for Anti-WT1 antibody		X[c]			X[c]		X[c,k]		X	
Blood sample for retrospective biomarker analyses		X[c]			X[c]		X[c,k]		X	

Table 4: Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study – Part 1 (Continued)

	Consolidation Phase[a,b]						**Maintenance Phase[a,b]**	**End of Study[b]**		**Follow-up**
	6th dose	**7th dose**	**8th dose**		**9th dose**					
	Day 43 (±2)	**Day 57 (±2)**	**Day 71 (±2)**	**Day 83**	**Day 85 (±2)**	**Day 87**	**every 28 (+7) days**	**48 hours before End of Study Visit**	**within 28 days after last dose**	**every 3 months**
Blood sample for PBMC isolation									X	
IHC tumor samples									X[l]	
Tumor assessment		X[c,m]			X[c,n]		X[c,m]		X[m]	
Adverse events	→	→	→	→	→	→	→	→	→	
Concomitant medications	→	→	→	→	→	→	→	→	→	
Disease Progression/ Survival									X[o]	X[o]

Abbreviations: AML = acute myeloid leukemia, CA-125 = cancer antigen 125, CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, FSH = follicle-stimulating hormone, HLA = human leukocyte antigen, IHC = immunohistochemistry, irRC = immune-related response criteria, IWG = International Working Group response criteria in acute myeloid leukemia, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PET = positron-emission tomography, RT-PCR = reverse transcriptase-polymerase chain reaction, SPECT = single-photon emission computed tomography, WT1 = Wilms' tumor gene product 1

[a] Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.1).

[b] All patients should complete an End of Study visit within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy.

[c] Prior to study drug administration.

[d] Includes systolic and diastolic blood pressures, pulse, respirations rate, and oral body temperature.

[e] For females of child-bearing potential.

[f] See Section 22 (Appendix IV) for list of required laboratory tests at each visit.

[g] Perform DTH skin test injections approximately 48 hours (but no sooner than 24 hours) prior to the evaluation.

[h] Perform DTH skin test injections immediately before administration of study drug.

[i] Evaluation should be made on the planned dosing day, prior to study drug administration.

[j] Evaluation should be approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injection.

[k] Perform every 2nd dosing day starting after the 9th dose.

[l] Biopsy for tumor tissue samples after the last dose of study drug is not mandatory. Tumor samples will be obtained from all patients who provide consent. IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.

Footnotes continued on the next page.

[m] Tumor assessments will be by irRC for solid tumors, modified IWG for AML, and/or standard tumor markers as appropriate eg, CA-125 for ovarian carcinoma and quantitative RT-PCR for WT1 transcript for AML. Perform every 8 weeks after 1st dose or more frequently as clinically indicated. Tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the 1st dose. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug. For patients with AML if no other measurable disease then bone marrow aspirations/biopsies should follow the general post-transplant biopsy schedule or other clinical site guidelines. Progressive disease requires confirmation by a repeat, consecutive assessment at least 4 weeks after the date of first documentation, unless rapid clinical deterioration is seen. For patients with glioblastoma, progressive disease should additionally be confirmed by SPECT, perfusion MRI, MRI spectroscopy or C-14 methionine PET or pathology from available surgical/biopsy specimens to differentiate from pseudoprogression. For patients with ovarian cancer that express CA-125, progressive disease should additionally be confirmed by CA-125 (≥ 2x higher of ULN or on study nadir). For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least at every 4 weeks or more frequently as clinically indicated.

[n] Tumor markers drawn from peripheral blood samples should be assessed at least every 4 weeks after the 1st dose but may be performed more frequently (For other tumor assessments, perform every 8 weeks after 1st dose or more frequently as clinically indicated).

[o] Following the End of Study visit, patients will be contacted every 3 months to evaluate disease progression, if not already reached, and survival.

Table 5: Schedule of Assessments for Screening and Vaccine Induction Phase – Part 2

	Screening		Vaccine Induction Phase[a,b,t]												
	within 21 days before 1st dose (-1 - -21)	within 7 days before 1st dose (-1 - -7)		1st dose		2nd dose	3rd dose	4th dose		5th dose		6th dose	7th dose	8th dose	9th dose
			Day -2	Day 1 (-1)	Day 3	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 27	Day 29 (-1)	Day 31	Day 36 (-1)	Day 43 (-1)	Day 50 (-1)	Day 57 (-1)
Informed consent	X														
Inclusion/exclusion	X	X													
Continuation criteria				X[c]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
Study drug administration				X		X	X	X		X		X	X	X	X
Medical history	X														
Physical exam		X		X[c]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
Height		X													
Weight		X		X[c]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
Vital Signs[d]		X		X[c]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
ECOG performance status		X		X[c]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
HLA typing[e]	X														
Serum pregnancy test[f]	X			X[c]											
Serology[g]	X														
Hematology/ serum chemistry[h]		X		X[c,i]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
Urinalysis		X		X[c,i]			X[c]			X[c]			X[c]		X[c]
12-lead ECG		X		X[c,i]						X[c]					X[c]

Table 5: Schedule of Assessments for Screening and Vaccine Induction Phase – Part 2 (Continued)

	Screening		Vaccine Induction Phase[a,b,t]												
	within 14/21 days before 1st dose (-1 – -14/-21)	within 7 days before 1st dose (-1 - -7)		1st dose		2nd dose	3rd dose	4th dose		5th dose		6th dose	7th dose	8th dose	9th dose
			Day -2	Day 1 (-1)	Day 3	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 27	Day 29 (-1)	Day 31	Day 36 (-1)	Day 43 (-1)	Day 50 (-1)	Day 57 (-1)
DTH skin test injection			X[j]	X[j,k]					X[j]	X[j,k]					
DTH skin test evaluation[l]				X[m]	X[n]					X[m]	X[n]				
Blood sample for CTL		X		X[c]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]
Blood sample for Anti-WT1 antibody				X[c]			X[c]			X[c]					X[c]
Blood sample for PBMC isolation				X[c]						X[c]					
Blood sample for retrospective biomarker analyses				X[c,o]	X[o]	X[c]	X[c]			X[c]					X[c]
IHC tumor samples		X[p,q]													
Tumor assessment	X[r]									X[c,s]					X[c,r]
Adverse events	→														
Concomitant medications	→														

Abbreviations: AML = acute myeloid leukemia, CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, FSH = follicle-stimulating hormone, HLA = human leukocyte antigen, IHC = immunohistochemistry, irRC = immune-related response criteria, IWG = International Working Group response criteria in acute myeloid leukemia, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PET = positron-emission tomography, RT-PCR = reverse transcriptase-polymerase chain reaction, SPECT = single-photon emission computed tomography, WT1 = Wilms' tumor gene product 1

Footnotes provided on the next page.

[a] Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.2).
[b] All patients should complete an End of Study visit (see Table 6) within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy.
[c] Prior to study drug administration.
[d] Includes systolic and diastolic blood pressures, pulse, respirations rate, and oral body temperature.
[e] If HLA typing has been performed previously, these results may be used, otherwise HLA typing should be the first procedure performed during screening.
[f] For females of child-bearing potential.
[g] Includes hepatitis B and C, human immunodeficiency virus (HIV)-1, and HIV-2, if there are signs or symptoms suggestive of infection.
[h] See Section 22 (Appendix IV) for list of required laboratory tests at each visit.
[i] Assessment may be omitted if an assessment was performed within the previous 3 days. If there are multiple assessments the most recent ones should be used.
[j] Perform DTH skin test injections approximately 48 hours (but no sooner than 24 hours) prior to the evaluation.
[k] Perform DTH skin test injections immediately before administration of study drug.
[l] If the DTH reactivity results in erythema with induration greater than 2 cm, or leads to ulceration of the skin test site, further DTH testing should not be conducted for the patient.
[m] Evaluation should be made on the planned dosing day, prior to study drug administration.
[n] Evaluation should be approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injection.
[o] Samples obtained 6 hours (± 30 minutes) and 48 hours (± 6 hours) postdose.
[p] In place of tumor tissue samples from a biopsy during screening, archived tumor tissue samples may be provided. Availability of tumor tissue samples should be determined during screening through provision of the accession number or other identification number. If necessary, the tumor tissue sample biopsy should be performed after study eligibility has been confirmed and before the first dose of study drug. The tumor tissue samples will only be provided to the sponsor for patients who receive study drug. In place of archival tumor tissue samples, patients with AML should have available a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. Patients with AML should also have peripheral blood assessed for blasts and WT1 transcript.
[q] IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.
[r] Tumor assessments (per irRC for solid tumors, modified IWG for AML, and/or standard tumor markers as appropriate, and quantitative RT-PCR for WT1 transcript for AML) are not required to be repeated if they have been performed within the 28 days before first dose (there are no variations allowed beyond this window). If multiple assessments are available, the most recent ones should be used as the baseline result. Data from at least one additional historical assessment prior to the baseline assessment should also be provided, if available. Progressive disease requires confirmation by a repeat, consecutive assessment at least 4 weeks after the date of first documentation, unless rapid clinical deterioration is seen. For patients with glioblastoma, progressive disease should additionally be confirmed by SPECT, perfusion MRI, MRI spectroscopy or C-14 methionine PET or pathology from available surgical/biopsy specimens to differentiate from pseudoprogression. For patients with AML, bone marrow aspirations/biopsies are to be provided at baseline and subsequently when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at baseline and at least every 4 weeks or more frequently as clinically indicated.
[s] Tumor markers drawn from peripheral blood samples should be assessed at least every 4 weeks after the first dose but may be performed more frequently to assess response and adjust study drug administration frequency (For other tumor assessments, perform every 8 weeks after first dose or more frequently as clinically indicated).
[t] Patients who do not complete the extended dosing in the Induction Phase for reasons other than intercurrent medical conditions may continue in the study and start dosing in the Consolidation phase as scheduled on Day 71, at the discretion of the investigator and the sponsor.

Table 6: Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study – Part 2

Consolidation Phase[a,b,p]									Maintenance Phase[a,b]	End of Study[b]		Follow-up
	10th dose		11th dose		12th dose	13th dose	14th dose	15th dose				
	Day 71 (±2)	Day 83	Day 85 (±2)	Day 87	Day 99 (±2)	Day113 (±2)	Day 127 (±2)	Day 141 (±2)	every 28 (+7) days	48 hours before End of Study Visit	within 28 days after last dose	every 3 months
Continuation criteria	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]			
Study drug administration	X		X		X	X	X	X	X			
Physical exam	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
Weight	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
Vital Signs[d]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
ECOG performance status	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
Serum pregnancy test[e]											X	
Hematology/ serum chemistry[f]	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
Urinalysis	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
12-lead ECG			X[c]			X[c]		X[c]	X[c]		X	
DTH skin test injection		X[g]	X[g,h]							X[g]		
DTH skin test evaluation			X[i]	X[j]							X[j]	

Table 6: Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study – Part 2 (Continued)

	Consolidation Phase[a,b,p]								Maintenance Phase[a,b]	End of Study[b]		Follow-up
	10th dose		11th dose		12th dose	13th dose	14th dose	15th dose				
	Day 71 (±2)	Day 83	Day 85 (±2)	Day 87	Day 99 (±2)	Day113 (±2)	Day 127 (±2)	Day 141 (±2)	every 28 (+7) days	48 hours before End of Study Visit	within 28 days after last dose	every 3 months
Blood sample for CTL	X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]		X	
Blood sample for Anti-WT1 antibody			X[c]			X[c]		X[c]	X[c,k]		X	
Blood sample for retrospective biomarker analyses			X[c]			X[c]		X[c]	X[c,k]		X	
Blood sample for PBMC isolation											X	
IHC tumor samples											X[l]	
Tumor assessment			X[c,n]			X[c,m]		X[c,n]	X[c,m]		X[m]	
Adverse events	→											
Concomitant medications	→											
Disease Progression/ Survival											X[o]	X[o]

Abbreviations: AML = acute myeloid leukemia, CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, FSH = follicle-stimulating hormone, HLA = human leukocyte antigen, IHC = immunohistochemistry, irRC = immune-related response criteria, IWG = International Working Group response criteria in acute myeloid leukemia, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PET = positron-emission tomography, RT-PCR = reverse transcriptase-polymerase chain reaction, SPECT = single-photon emission computed tomography, WT1 = Wilms' tumor gene product 1

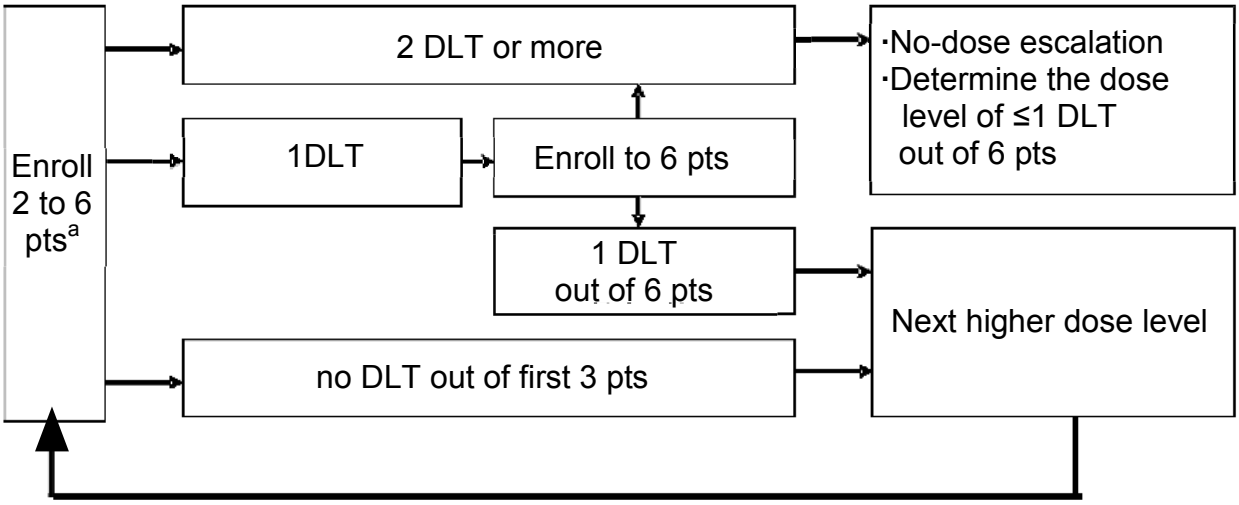
Footnotes provided on the next page.

[a] Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.2).
[b] All patients should complete an End of Study visit within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy.
[c] Prior to study drug administration.
[d] Includes systolic and diastolic blood pressures, pulse, respirations rate, and oral body temperature.
[e] For females of child-bearing potential.
[f] See Section 22 (Appendix IV) for list of required laboratory tests at each visit.
[g] Perform DTH skin test injections approximately 48 hours (but no sooner than 24 hours) prior to the evaluation.
[h] Perform DTH skin test injections immediately before administration of study drug.
[i] Evaluation should be made on the planned dosing day, prior to study drug administration.
[j] Evaluation should be approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injection.
[k] Perform every second dosing day during the Maintenance Phase.
[l] Biopsy for tumor tissue samples after the last dose of study drug is not mandatory. Tumor samples will be obtained from all patients who provide consent. IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.
[m] Tumor assessments will be by irRC for solid tumors, modified IWG for AML, and/or standard tumor markers as appropriate, and quantitative RT-PCR for WT1 transcript for AML. Perform every 8 weeks after first dose or more frequently as clinically indicated. Tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the first dose. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug. For patients with AML if no other measurable disease then bone marrow aspirations/biopsies should follow the general post-transplant biopsy schedule or other clinical site guidelines. Progressive disease requires confirmation by a repeat, consecutive assessment at least 4 weeks after the date of first documentation, unless rapid clinical deterioration is seen. For patients with glioblastoma, progressive disease should additionally be confirmed by SPECT, perfusion MRI, MRI spectroscopy or C-14 methionine PET or pathology from available surgical/biopsy specimens to differentiate from pseudoprogression. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least every 4 weeks or more frequently as clinically indicated.
[n] Tumor markers drawn from peripheral blood samples should be assessed at least every 4 weeks after the first dose but may be performed more frequently (For other tumor assessments, perform every 8 weeks after first dose or more frequently as clinically indicated).
[o] Following the End of Study visit, patients will be contacted every 3 months to evaluate disease progression, if not already reached, and survival.
[p] The Consolidation Phase includes a maximum of 6 doses. Patients who do not complete the extended dosing in the Consolidation Phase for reasons other than intercurrent medical conditions may continue in the study and start dosing in the Maintenance phase as scheduled on Day 169, at the discretion of the investigator and the sponsor.

7.2. Dose Level Escalation

The planned dose level escalation scheme for Part 1 is presented in Figure 3 and for Part 2 is presented in Figure 4.

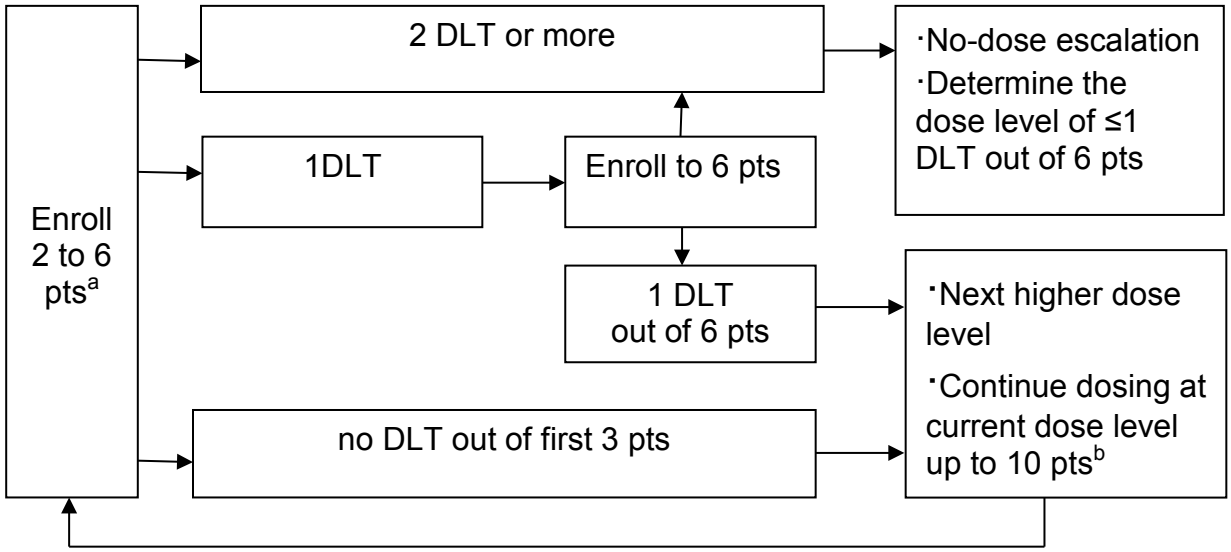
Figure 3: Dose Escalation Scheme – Part 1



Abbreviations: DLT = dose-limiting toxicity, pts = patients

[a] The initial patients in the each dose escalation cohort will be enrolled at least one week apart to evaluate initial safety from the first 2 patients; after which, if initial acceptable safety has been observed, there is no requirement to wait between enrolling individual patients within a cohort.

Figure 4: Dose Escalation Scheme – Part 2



Abbreviations: DLT = dose-limiting toxicity, pts = patients

[a] The initial patients in the each dose escalation cohort will be enrolled at least one week apart to evaluate initial safety from the first 2 patients; after which, if initial acceptable safety has been observed, there is no requirement to wait between enrolling individual patients within a cohort.

[b] If additional patients are ready to enroll in the study prior to completion of the DLT Evaluation Period for the 27.0 mg dose cohort, up to a total of 10 patients may be enrolled at the 18.0 mg dose level. At least 4 patients with each malignancy type (glioblastoma and acute myeloid leukemia [AML]) will be enrolled at each of these dose levels. If the MTD is reached in Part 2 before the total of 20 patients are enrolled, remaining patients will be enrolled at the prior dose level.

The initial patients in each dose escalation cohort will be enrolled at least one week apart to evaluate initial safety from the first 2 patients; after which, if initial acceptable safety has been observed, there is no requirement to wait between enrolling individual patients within a cohort.

After completion of DLT evaluation for the first dose cohort, if the study continues, enrollment of subsequent patients will be conducted sequentially in subsequent dose escalation cohorts and continue until the MTD or all planned cohorts are attained in the dose escalation parts of the study.

The 0.3 mg dose cohort will be conducted first in Part 1. If after 3 patients in this dose cohort have completed the DLT Evaluation Period and there are no DLTs identified, enrollment of the subsequent cohort will begin. If additional patients are ready to enroll in the study prior to completion of the DLT Evaluation Period for the first 3 patients in the 0.3 mg dose cohort, up to 3 more patients may be enrolled in that cohort.

Again, in subsequent dose escalation cohorts in Part 1, if 3 patients in a dose cohort complete the DLT Evaluation Period and there are no DLTs identified, then the dose level is increased, otherwise enrollment of additional patients (up to 3 more) may be permitted in the same cohort. If one of 3 patients in a dose escalation cohort experiences a DLT then up to a total of 6 patients are enrolled in the same dose cohort and dose escalation may only proceed if no additional patients experience DLT. Patients not evaluable for DLT assessment may be replaced.

In Part 2 of the study, the 18.0 mg cohort will be conducted first. If 3 patients in the dose cohort complete the DLT Evaluation Period and there are no DLTs identified, then the 27.0 mg dose cohort may begin, otherwise enrollment of additional patients (up to 3 more) may be permitted in the same cohort. If one of 3 patients in a dose escalation cohort experiences a DLT then up to a total of 6 patients are enrolled in the same dose cohort and dose escalation may only proceed if no additional patients experience DLT. After safety and tolerability have been established for the 18.0 mg cohort, enrollment of subsequent patients will be conducted sequentially in the 27.0 mg cohort. If additional patients are ready to enroll in the study prior to completion of the DLT Evaluation Period for the 27.0 mg dose cohort, up to a total of 10 patients may be enrolled at the 18.0 mg dose level. Approximately 10 patients at each dose level (18.0 and 27.0 mg) with at least 4 patients with each malignancy type (glioblastoma and AML) will be enrolled. If the MTD is reached in Part 2 before the total of 20 patients are enrolled, remaining patients will be enrolled at the prior dose level. Patients not evaluable for DLT assessment may be replaced.

If at any time during dose escalation 2 or more patients experience DLT within a dose cohort that suggests that the MTD has been exceeded; no additional patients will be enrolled into that dose cohort and dose escalation will end. The MTD will be the dose level below that which resulted in 2 or more patients experiencing a DLT. If the suspected MTD is based on a cohort in which fewer than 6 patients were enrolled then additional patients will be enrolled and treated at that dose level until there is a total of 6 patients evaluable for DLT within that dose escalation cohort.

In the event that a dose level is excluded from further study due to dose limiting toxicity all patients may continue the study at the most recently completed dose without DLT, eg, if the 27.0 mg dose is excluded due to DLT all patients may continue at 18.0 mg.

7.2.1. Criteria for Dose-limiting Toxicity

Dose-limiting toxicities are defined as any Grade 3 or greater AE that occurs after the administration of study drug during the DLT Evaluation Period that are not related to underlying disease, intercurrent illness, or concomitant medications (Changes in hematology parameters need to have been confirmed on repeat assessment and constitute at least a 2 grade shift. Grade 3 AEs of nausea, vomiting, and fatigue that are common and manageable in cancer patients will not be considered DLT if they can be ameliorated to < Grade 3 with standard supportive care management.).

The DLT Evaluation Period extends from the day of the first dose of study drug to just prior to the fifth dose (Days 1 - 29). No more than 4 doses of study drug will be administered during the DLT Evaluation Period.

In a dose cohort with less than 2 patients with DLT, a minimum of 3 evaluable patients are needed to assess dose level escalation. An evaluable patient is defined as a patient who has a DLT or a patient who completes the DLT Evaluation Period without the occurrence of a DLT.

Patients who discontinue from the study for a reason other than DLT prior to completion of the DLT Evaluation Period are not evaluable for DLT and will be replaced.

7.2.2. Reporting of Dose-limiting Toxicity or Completion of DLT Evaluation Period

If a DLT occurs, the investigator or his designee must complete the DLT form with the requested information describing the DLT and fax or email the form to Sunovion Pharmaceuticals Inc. or its agent within 1 business day of becoming aware of the DLT.

When a patient completes the DLT Evaluation Period, the investigator or his designee must complete the DLT form to confirm no DLT has occurred and fax or email the form to Sunovion Pharmaceuticals Inc. or its agent within 1 business day of the patient completing the DLT Evaluation Period.

The DLT form will be provided as a part of the document package necessary to conduct this clinical study.

7.3. Dose-Level Escalation Stopping Criteria

The MTD is defined as the dose at which no more than 1 of 6 patients experiences a DLT when 2 of 2 to 6 patients experiences a DLT at the next higher dose level.

Part 1

Dose level escalation will be completed when the MTD has been determined or the minimum number of patients has been enrolled at the highest planned dose level to meet dose escalation or MTD criteria (2-6 patients).

Additional dose escalation cohorts after the initial expansion cohorts may be enrolled if a MTD has not been determined and significant signs of toxicity have not been observed in the expansion cohorts.

Part 2

Dose level escalation will be completed when 20 patients have been enrolled.

7.4. Dose Adjustment Criteria

The following sections provide guidelines for intra-patient dose adjustment. Dose level escalation among cohorts of patients is described in Section 7.2.

7.4.1. Dose Reduction Criteria

The following guidelines are provided for dose level reductions:

- Dose reduction from the lowest dose level (0.3 mg) is not permitted at any time.
- Patients who experience DLT may remain on the study at a reduced dose, if they are deriving some therapeutic benefit from study drug and meet the continuation criteria for subsequent dosing (see Section 8.3.2). These decisions will be addressed on a case by case basis. The dose will be reduced one level, eg, from 0.9 to 0.3 mg. Patients who require reduction from this reduced dose will be discontinued from receiving further study drug.

After the DLT Evaluation Period, if a patient experiences a study drug-related Grade 3 toxicity, there will be a review of safety data to determine appropriate dosing for that patient and other patients on study, as well as for any subsequently enrolled patients.

In the event that a Grade 4 or greater toxicity is reported during the study, the sponsor and the investigator will conduct a thorough evaluation of the available safety data to decide whether to continue enrolling new patients into the study.

Dose delays are described in Section 8.3.2.

7.4.2. Dose Increases

Patients who have completed the consolidation phase of their assigned cohort and have not experienced a DLT, ≥ Grade 2 study drug-related injection-site reaction, or required a dose reduction may have their dose escalated to that of the highest cohort for which safety and tolerability have been established. This includes patients from Part 1 of the study having their dose escalated to a Part 2 dose.

7.5. Prevention of Missing Data

In an effort to minimize the number of patients who withdraw consent prior to completion of the DLT Evaluation Period, the number of assessments has been limited to those required to collect the information needed to address the objectives of the study.

7.6. Study Termination Criteria

The study may be terminated at any time by the sponsor for any reason.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

8.1.1. Patient Inclusion Criteria – Part 1

To qualify for participation in Part 1 of the study, patients must meet all of the following inclusion criteria:

1. Patient or his or her legal representatives must give written informed consent and privacy authorization prior to participation in the study.
2. Patient must be willing and able to comply with the study procedures and visit schedules and must be able to follow verbal and written instructions.
3. Patient must be ≥ 18 years of age.
4. Women of childbearing potential and men with female sexual partners of childbearing potential must agree to abstain from sexual intercourse or use a double barrier method of contraception (eg, condom + diaphragm) for the duration of study participation. Note: The definition of menopause from the NCCN Clinical Practice Guidelines for Invasive Breast Cancer (Version 1.2012) should be followed to determine if a woman is of childbearing potential (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).
5. Patient must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0, 1, or 2 (refer to Appendix II).
6. Patient has a life expectancy of at least 4 months.
7. Patient must have one of the following histologically or cytologically documented measurable (may be measurable by tumor markers only, such as quantitative RT-PCR for WT1 transcript for AML, or CA-125 for ovarian carcinoma) advanced stage malignancies: non-small cell lung, ovarian, glioblastoma, and AML (not including acute promyelocytic leukemia), known to overexpress the WT1 protein. Note: Determination of WT1 expression will not be assessed prior to patient enrollment.
8. Patient must have an advanced stage malignancy defined as meeting at least one of the following criteria:
    - progressed or recurred despite standard therapy
    - no standard therapy exists
    - patient is intolerant of standard therapy
    - patient is not a candidate for standard therapy
9. Patient must be HLA-A*0201+ and/or HLA-A*0206+
10. Patient must have adequate bone marrow and immune reserve, as documented by:
    - Absolute neutrophil count (ANC) ≥ 1,000/µl

- Platelet count ≥ 10.0 x 10^4/µl (≥ 5.0 x 10^4/µl after stem cell transplant)
- Hemoglobin ≥ 9.0 g/dL
- Absolute lymphocyte count (ALC) ≥ 1,000/µl (≥ 500/µl after stem cell transplant)

Note: After completion of dose escalation, patients with AML are not required to meet these hematologic criteria.

11. Patient must have adequate renal function documented by a serum creatinine of ≤ 1.5 times the upper limit of normal (ULN) for the reference lab.
12. Patient must have adequate hepatic function documented by a total bilirubin of ≤ 2.0 mg/dl (≤ 3.0 mg/dl for patients with known Gilbert's syndrome) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the ULN for the reference lab.
13. Patient must have access to archival tumor tissue sample or agree to undergo biopsy after study eligibility has been confirmed to obtain fresh sample for evaluation of WT1 expression. In place of archival tumor tissue samples, patients with AML should have available a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. Note: The archived tumor tissue sample does not need to be delivered to the clinical site prior to enrollment of the patient, however its availability should be confirmed through provision of the accession number or other identification number.

8.1.2. Patient Inclusion Criteria - Part 2

To qualify for participation in Part 2 of the study, patients must meet all of the following inclusion criteria:

1. Patient or his or her legal representatives must give written informed consent and privacy authorization prior to participation in the study.
2. Patient must be willing and able to comply with the study procedures and visit schedules and must be able to follow verbal and written instructions.
3. Patient must be ≥ 18 years of age.
4. Women of childbearing potential and men with female sexual partners of childbearing potential must agree to abstain from sexual intercourse or use a double barrier method of contraception (eg, condom + diaphragm) for the duration of study participation. Note: The definition of menopause from the NCCN Clinical Practice Guidelines for Invasive Breast Cancer (Version 1.2012) should be followed to determine if a woman is of childbearing potential (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).
5. Patient must have an ECOG Performance Score of 0, 1, or 2 (refer to Appendix II).
6. Patient has a life expectancy of at least 4 months.
7. Patient must have histologically or cytologically documented measurable (may be measurable by tumor markers only, such as quantitative RT-PCR for WT1 transcript for AML) advanced stage glioblastoma or AML (not including acute promyelocytic

leukemia), known to overexpress the WT1 protein. Note: Determination of WT1 expression will not be assessed prior to patient enrollment.

8. Patient must have an advanced stage malignancy defined as meeting at least one of the following criteria:
   - progressed or recurred despite standard therapy
   - no standard therapy exists
   - patient is intolerant of standard therapy
   - patient is not a candidate for standard therapy
9. Patient must be HLA-A*0201+ and/or HLA-A*0206+.
10. Patient with glioblastoma must have adequate bone marrow and immune reserve, as documented by:
    - ANC ≥ 100/µl (≥ 500/µl after stem cell transplant)
    - Platelet count ≥ 10.0 x 10^4/µl (≥ 5.0 x 10^4/µl after stem cell transplant)
    - Hemoglobin ≥ 9.0 g/dL
    - ALC ≥ 900/µl

    Note: Patients with AML are not required to meet these hematologic criteria.
11. Patient must have adequate renal function documented by a serum creatinine of ≤ 1.5 times the ULN for the reference lab.
12. Patient must have adequate hepatic function documented by a total bilirubin of ≤ 2.0 mg/dl (≤ 3.0 mg/dl for patients with known Gilbert's syndrome) and ALT and AST ≤ 3 times the ULN for the reference lab.
13. Patient must have access to archival tumor tissue sample or agree to undergo biopsy after study eligibility has been confirmed to obtain fresh sample for evaluation of WT1 expression. In place of archival tumor tissue samples, patients with AML should have available a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. Note: The archived tumor tissue sample does not need to be delivered to the clinical site prior to enrollment of the patient, however its availability should be confirmed through provision of the accession number or other identification number.
14. Patients with AML must be willing to undergo bone marrow aspiration/biopsy during treatment if there are no other indicators of measureable disease.

8.2. Patient Exclusion Criteria

8.2.1. Patient Exclusion Criteria – Part 1

To qualify for participation in Part 1 of the study, patients must not meet any of the following exclusion criteria:

1. Patient has an extensively disseminated primary glioblastoma.

2. Patient has symptomatic brain metastases, ie, presence of neurological symptoms or requiring treatment with corticosteroids, or central nervous system (CNS) leukemia.
3. Patient has an infection requiring treatment with systemic antibiotics or antiviral medication or has completed treatment for such an infection within 4 days prior to planned first dose of study drug.
4. Patient requires systemic, pharmacologic doses of corticosteroids (equivalent to > 60 mg hydrocortisone/day or 2 mg dexamethasone/day). Replacement doses (equivalent to ≤ 5 mg prednisone/day), and topical, ophthalmic, and inhalation steroids are permitted as needed.
5. Patient has a positive test for Hepatitis B surface antigen, Hepatitis C antibody, human immunodeficiency virus (HIV)-1, or HIV-2 antibody, or has a history of a positive result.
6. Patient has received any of the following treatments within the specified timeframe:
   - endocrine therapy, immunotherapy, transfusion, or hematopoietic factors within 14 days prior to planned first dose of study drug (Note: After completion of dose escalation, patients with AML are not required to meet these hematologic criteria, eg. transfusions and hematopoietic growth factors.),
   - chemotherapy including molecular-targeting therapy within 21 days prior to planned first dose of study drug (for molecular-targeted agents that are not associated with myelosuppression or immunosuppression, the minimum interval is 5 half-lives if that is less than 21 days),
   - surgery, radiation, or immunosuppressants within 28 days prior to planned first dose of study drug,
   - investigational drug within the 28 days prior to planned first dose of study drug, or
   - mitomycin-C or nitrosoureas within 42 days prior to planned first dose of study drug.

     Note: Patient receiving luteinizing hormone-releasing hormone [LHRH] agonists or antagonists or antiestrogens or aromatase inhibitors started and at a stable dose for at least 90 days prior to planned first dose of study drug is eligible.
7. Patient has an unresolved ≥ Grade 2 AE from a previous antineoplastic treatment, excluding alopecia.
8. Woman who is pregnant or lactating or has a positive pregnancy test at screening. If a woman has a positive pregnancy test, further evaluation may be conducted to rule out ongoing pregnancy to allow the patient to be eligible.
9. Patient has an autoimmune condition, including, but not limited to, multiple sclerosis, Grave's disease, vasculitis, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, myasthenia gravis, ankylosing spondylitis, Wegener's granulomatosis, ulcerative colitis, Crohn's disease, psoriasis requiring systemic therapy, pemphigus, temporal arteritis, dermatomyositis, Sjögren's syndrome, Goodpasture's syndrome, interstitial pneumonitis, interstitial nephritis, or Henoch-Schönlein purpura.
10. Patient has in the opinion of the investigator any intercurrent conditions that could preclude their participation in the study, pose an undue medical hazard, or that could

interfere with the interpretation of the study results, including, but not limited to, patients with congestive heart failure (New York Heart Association [NYHA] Class III or IV; refer to Appendix III), unstable angina, cardiac arrhythmia requiring treatment, recent (within the prior 6 months) myocardial infarction, acute coronary syndrome or stroke, severe obstructive pulmonary disease, hypertension requiring more than 2 medications for adequate control, or diabetes mellitus with more than 2 episodes of ketoacidosis in the prior 12 months.

11. Patient has pleural effusion, ascites, or pericardial fluid requiring drainage. Note: Patient who had drain removal ≥ 14 days prior to planned first dose of study drug and has no sign of worsening is eligible.
12. Patient has any other medical, psychiatric, or social condition, including substance abuse that in the opinion of the investigator would preclude participation in the study.
13. Patient has had previous treatment with the study drug or other WT1-related vaccine therapy.
14. Patient has a known hypersensitivity to any of the components of the study drug.
15. Patient is a staff member of the sponsor or clinical site and is involved in the conduct of the study or the relative of such a staff member.

8.2.2. Patient Exclusion Criteria – Part 2

To qualify for participation in Part 2 of the study, patients must not meet any of the following exclusion criteria:

1. Patient has an extensively disseminated primary glioblastoma.
2. Patient has symptomatic brain metastases, ie, presence of neurological symptoms or requiring treatment with corticosteroids, or CNS leukemia.
3. Patient has an infection and has had a body temperature of > 38.3˚C within 48 hours prior to planned first dose of study drug.
4. Patient requires systemic, pharmacologic doses of corticosteroids (equivalent to > 60 mg hydrocortisone/day or 2 mg dexamethasone/day). Replacement doses (equivalent to ≤ 5 mg prednisone/day), and topical, ophthalmic, and inhalation steroids are permitted as needed.
5. Patient has a positive test for Hepatitis B surface antigen, Hepatitis C antibody, HIV-1, or HIV-2 antibody, or has a history of a positive result.
6. Patient has received any of the following treatments within the specified timeframe:
   - endocrine therapy, immunotherapy, transfusion, or hematopoietic factors within 14 days prior to planned first dose of study drug (Note: Patients with AML are not required to meet these hematologic criteria, eg, transfusions and hematopoietic growth factors.),
   - chemotherapy including molecular-targeting therapy within 21 days prior to planned first dose of study drug (for molecular-targeted agents that are not associated with

myelosuppression or immunosuppression, the minimum interval is 5 half-lives if that is less than 21 days),

- surgery, radiation, or immunosuppressants within 28 days prior to planned first dose of study drug,
- investigational drug within the 28 days prior to planned first dose of study drug, or
- mitomycin-C or nitrosoureas within 42 days prior to planned first dose of study drug.

Note: Patient receiving LHRH agonists or antagonists or antiestrogens or aromatase inhibitors started and at a stable dose for at least 90 days prior to planned first dose of study drug is eligible. Patients are permitted one 28 day cycle of concurrent treatment with hydroxyurea during the study.

7. Patient has an unresolved ≥ Grade 2 AE from a previous antineoplastic treatment, excluding alopecia.
8. Woman who is pregnant or lactating or has a positive pregnancy test at screening. If a woman has a positive pregnancy test, further evaluation may be conducted to rule out ongoing pregnancy to allow the patient to be eligible.
9. Patient has an autoimmune condition, including, but not limited to, multiple sclerosis, Grave's disease, vasculitis, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, myasthenia gravis, ankylosing spondylitis, Wegener's granulomatosis, ulcerative colitis, Crohn's disease, psoriasis requiring systemic therapy, pemphigus, temporal arteritis, dermatomyositis, Sjögren's syndrome, Goodpasture's syndrome, interstitial pneumonitis, interstitial nephritis, or Henoch-Schönlein purpura.
10. Patient has in the opinion of the investigator any intercurrent conditions that could preclude their participation in the study, pose an undue medical hazard, or that could interfere with the interpretation of the study results, including, but not limited to, patients with congestive heart failure (NYHA Class III or IV; refer to Appendix III), unstable angina, cardiac arrhythmia requiring treatment, recent (within the prior 6 months) myocardial infarction, acute coronary syndrome or stroke, severe obstructive pulmonary disease, hypertension requiring more than 2 medications for adequate control, or diabetes mellitus with more than 2 episodes of ketoacidosis in the prior 12 months.
11. Patient has pleural effusion, ascites, or pericardial fluid requiring drainage. Note: Patient who had drain removal ≥ 14 days prior to planned first dose of study drug and has no sign of worsening is eligible.
12. Patient has any other medical, psychiatric, or social condition, including substance abuse that in the opinion of the investigator would preclude participation in the study.
13. Patient has had previous treatment with the study drug or other WT1-related vaccine therapy.
14. Patient has a known hypersensitivity to any of the components of the study drug.
15. Patient is a staff member of the sponsor or clinical site and is involved in the conduct of the study or the relative of such a staff member.

8.3. Continuation Criteria

8.3.1. Enrollment – Part 1 and Part 2

In order to receive the first dose of study drug on Day 1, patients must continue to meet all inclusion (see Section 8.1) and no exclusion criteria (see Section 8.2).

8.3.2. Subsequent Dosing

8.3.2.1. Subsequent Dosing – Part 1

Patients are eligible to continue dosing at each subsequent dosing day if they meet the following criteria, have not met any of the discontinuation criteria (see Section 12.2), and can receive the next dose of study drug during the prespecified timeframe:

- ANC $\geq$ 750/µl
- Platelet count $\geq 5.0 \times 10^4$/µl ($\geq 3.5 \times 10^4$/µl after stem cell transplant)
- All non-hematologic toxicity resolved to at least Grade 2 or to pretreatment levels

Note: After completion of dose escalation, patients with AML are not required to meet these hematologic criteria.

For doses 2 through 5, the subsequent dose may be delayed 1 week (ie, the subsequent dose should be administered within 8 days after the intended dosing date inclusive of the day of planned dosing) to allow patients to recover from intercurrent medical conditions and meet these continuation criteria.

For doses 6 and beyond, the subsequent dose may be delayed 2 weeks (ie, the subsequent dose should be administered within 15 days after the intended dosing date inclusive of the day of planned dosing) to allow the patient to recover from intercurrent medical conditions and meet these continuation criteria.

Patients who cannot receive the next dose of study drug within the specified timeframes provided above must be discontinued from receiving further study drug.

8.3.2.2. Subsequent Dosing – Part 2

Patients are eligible to continue dosing at each subsequent dosing day if they meet the following criteria, have not met any of the discontinuation criteria (see Section 12.2), and can receive the next dose of study drug during the prespecified timeframe:

- ANC $\geq$ 750/µl ($\geq$ 500/µl after stem cell transplant)
- Platelet count $\geq 5.0 \times 10^4$/µl ($\geq 3.5 \times 10^4$/µl after stem cell transplant)
- All non-hematologic toxicity resolved to at least Grade 2 or to pretreatment levels

Note: Patients with AML are not required to meet these hematologic criteria.

During the Induction Phase, the subsequent dose may be delayed 1 week (ie, the subsequent dose should be administered within 8 days after the intended dosing date inclusive of the day of planned dosing) to allow patients to recover from intercurrent medical conditions and meet these continuation criteria.

During the Consolidation and Maintenance Phases, the subsequent dose may be delayed 2 weeks (ie, the subsequent dose should be administered within 15 days after the intended dosing date inclusive of the day of planned dosing) to allow the patient to recover from intercurrent medical conditions and meet these continuation criteria.

Patients who cannot receive the next dose of study drug within the specified timeframes provided above may continue in the study at the discretion of the investigator and the sponsor.

Patients who do not complete the extended dosing in the Induction Phase or the Consolidation Phase for reasons other than intercurrent medical conditions may continue in the study and start dosing in the next phase as scheduled at the discretion of the investigator and the sponsor.

9. TREATMENT OF PATIENTS

9.1. Concomitant Medications

Concomitant medication and therapy guidelines during the study are the same during Part 1 and Part 2 of the study except as indicated for hydroxyurea.

9.1.1. Disallowed Medications During Study

Due to the possibility of affecting the evaluation of safety or response to study drug, use of any of the following medications is prohibited during study participation from screening through the End of Study visit, unless other timing is noted.

- All other antineoplastic therapy including systemic radiopharmaceuticals, with the exception of LHRH agonists or antagonists or antiestrogens or aromatase inhibitors started and at a stable dose for at least 90 days prior to the planned first dose of study drug. See Section 9.1.2 regarding hydroxyurea use in Part 2 of the study.
- Other investigational agents
- Pharmacologic doses of systemic corticosteroids (equivalent to > 60 mg hydrocortisone/day or 2 mg dexamethasone/day). Note: Replacement doses (equivalent to ≤ 5 mg prednisone/day), and topical, ophthalmic, and inhalation corticosteroids are permitted as needed.
- Immunomodulatory therapy
- Systemic immunosuppressive therapy
- Treatment aimed at preventing the induction of AEs by the study drug. Note: Treatment to prevent the recurrence of an AE that has occurred previously on study is permitted.

9.1.2. Allowed Medications During Study

All intercurrent medical conditions should be treated by the investigator according to current community standards of care. Treatment to prevent the recurrence of an AE that has occurred previously on study is permitted. Patients may also receive medications for symptomatic relief, such as analgesics, laxatives, anti-emetics, hypnotics, etc.

Replacement doses of steroids (equivalent to ≤ 5 mg prednisone/day), and topical, ophthalmic, and inhalation corticosteroids are permitted as needed.

Local injection site reactions may be treated with dermal steroid treatment or topical nonsteroidal anti-inflammatory drugs.

In addition, in Part 2 of the study, one 28-day cycle of concurrent treatment with hydroxyurea is permitted.

9.1.3. Prohibited Therapies

Due to the possibility of affecting the evaluation of safety or response to study drug, use of any of the following therapies is prohibited during study participation from screening through the End of Study visit.

- Surgery for the treatment of neoplastic disease. Note: Palliative surgery for symptomatic lesion(s) is permitted as long as the lesion is not the only evaluable one.
- Radiation therapy for the treatment of neoplastic disease. Note: Palliative radiation therapy for symptomatic lesion(s) is permitted as long as the lesion is not the only evaluable one.
- Hyperthermia/thermotherapy for the treatment of neoplastic disease

9.1.4. Allowed Therapies

Palliative surgery and radiation therapy for symptomatic lesion(s) are permitted during the study as long as the lesion is not the only evaluable one. Study drug administration should be interrupted during and following these therapies until the patient has adequately recovered from the effects of treatment, in the investigator's judgment.

Transfusions are permitted.

9.2. Treatment Compliance

All patients will be administered study drug in-clinic; therefore treatment compliance will be documented by site personnel.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of Study Drug

The study drug contains 4 components that may be diluted prior to administration:

1. WT2725 Injection 50 mg/mL
2. WT2725 Injection 2 mg/mL
3. Diluting Solution for WT2725 Injection (DSWI)
4. W/O pre-Emulsion (WOPE)

WT2725 Injection 50 mg/mL and WT2725 Injection 2 mg/mL are sterile aqueous solutions containing WT2725, L-Methionine, Tartaric Acid, Sodium Hydroxide, and Water for Injection, and may also contain Hydrochloric Acid.

Diluting Solution for WT2725 Injection (DSWI) is a sterile aqueous solution containing L-Methionine, Tartaric Acid, Sodium Hydroxide, and Water for Injection, and may also contain Hydrochloric Acid.

W/O pre-Emulsion (WOPE) is a sterile water-in-oil emulsion containing Ethyl Oleate, 2-Octyldodecyl Myristate, Sorbitan Monooleate, Glyceryl Monooleate, Polyoxyl 20 Hydrogenated Castor Oil, Concentrated Glycerin, Sodium Dihydrogen Phosphate Dihydrate, and Water for Injection.

10.2. Study Drug Packaging and Labeling

WT2725 Injection (2 mg/mL and 50 mg/mL), Diluting Solution for WT2725 Injection (DSWI), and W/O pre-Emulsion (WOPE) are packaged in clear type 1 glass vials. The closure is a rubber stopper that forms a tight seal when crimp sealed with an aluminum over seal.

Each vial is labeled with a 1-panel open label. Fifty vials of each component are packaged into cartons with protective inserts. The cartons are also labeled with a 1-panel open label.

The vial labels for each of the 4 components will include the following information at a minimum:

- Protocol number
- Sponsor’s name and address
- Content
- Investigational New Drug statement
- Instructions for use and storage
- Lot number

The carton labels for each of the 4 components will be labeled with the following information at a minimum:

- Protocol number
- Sponsor's name and address
- Content
- Investigational New Drug statement
- Instructions for use and storage
- Lot number
- Blank space for site number and date opened

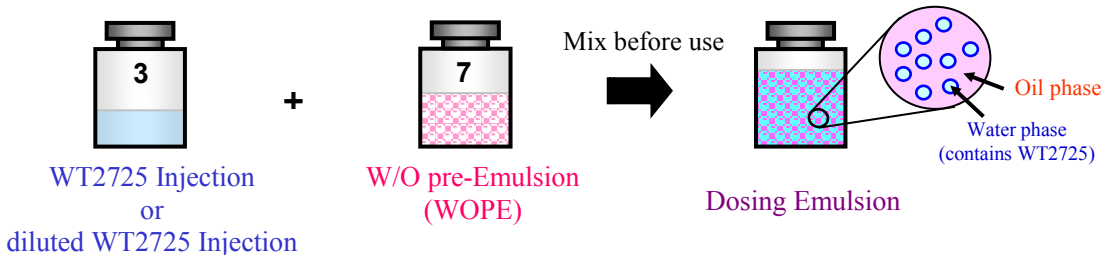
10.3. Study Drug Storage

All study drug components (WT2725 Injection 50 mg/mL, WT2725 Injection 2 mg/mL, Diluting Solution for WT2725 Injection [DSWI], and W/O pre-Emulsion [WOPE]) should be stored under refrigeration (cold temperature 2°C to 8°C), and protected from light and freezing.

10.4. Study Drug Preparation

At the clinical site, WT2725 Injection (2 mg/mL and/or 50 mg/mL) will be diluted to an appropriate concentration using DSWI, if needed. Subsequently, WT2725 Injection or diluted WT2725 Injection will be mixed with the WOPE at a ratio of 3:7 (by volume) to form the WT2725 Dosing Emulsion (Figure 5). WT2725 Dosing Emulsion is a white liquid emulsion and will be administered by sc injection.

Figure 5: Description of WT2725 Dosing Emulsion (Drug Product) Preparation



The following dosages are planned for Part 1 of the study:

- for DTH skin tests only - 0.01 mg WT2725 in diluted WT2725 Injection (0.05 mL x 1 site, id) and Control (Diluting Solution for WT2725 Injection [DSWI]) (0.05 mL x 1 site, id)
- 0.3 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)

- 0.9 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)
- 3.0 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)
- 9.0 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)

The following dosages are planned for Part 2 of the study:

- 18.0 mg WT2725 in Dosing Emulsion (0.6 mL x 2 sites for a total volume of 1.2 mL per patient, sc)
- 27.0 mg WT2725 in Dosing Emulsion (0.9 mL x 2 sites for a total volume of 1.8 mL per patient, sc)

All drug products must be prepared and stored under ambient conditions on the day of dosing, and used or discarded within 6 hours following preparation of the drug product. A brief description of study drug preparation is provided in Appendix VI.

10.5. Study Drug Administration

All open-label study drug will be administered at the study site by trained staff.

In Part 1 of the study, after safety and tolerability have been established for the 0.3 mg dose cohort (following completion of DLT Evaluation Period), enrollment of subsequent patients will be conducted sequentially in subsequent dose escalation cohorts and continue until the MTD or all planned cohorts are attained. This dose is considered the RP2D, and subsequent patients enrolled will initiate treatment at this dose. Additional dose escalation cohorts after the initial expansion cohorts may be enrolled if a MTD has not been determined and significant signs of toxicity have not been observed in the expansion cohorts. In Part 2 of the study, the 18.0 mg cohort will be conducted first. After safety and tolerability have been established for the 18.0 mg cohort, enrollment of subsequent patients will be conducted sequentially in the 27.0 mg cohort. If additional patients are ready to enroll in the study prior to completion of the DLT Evaluation Period for the 27.0 mg dose cohort, up to a total of 10 patients may be enrolled at the 18.0 mg dose level.

Each dose of study drug will be administered using 2 injection sites (eg, 0.3 mL/site x 2 for the 9.0 mg dose). The only restriction on the dosing site is that the forearm used for the DTH skin tests should not be used for administration of study drug. Wherever possible, injections should be administered into the area surrounding the regional lymph nodes in the upper arm, the lower abdomen, or the femoral area. Rotation of injection sites is permitted. Injection sites should not be chosen in the area of any ongoing skin condition, eg, area of psoriasis.

Each part of the study will include 3 treatment phases based on intended timing of study drug dosing as indicated below:

Part 1:

- Vaccine Induction Phase: once every 7 days for 4 weeks (doses 1 - 5)
- Consolidation Phase: once every 14 days for 6 weeks (doses 6 - 9)

- Maintenance Phase: once every 28 days until discontinuation (doses 10 and thereafter)

Part 2:

- Vaccine Induction Phase: once every 7 days for 8 weeks (doses 1 - 9)
- Consolidation Phase: once every 14 days for 10 weeks (doses 10 – 15 [maximum 6 doses])
- Maintenance Phase: once every 28 days until discontinuation (dose 16 and thereafter)

10.5.1. Assignment of Dose Cohort for Each Patient

The following steps will be followed to assign the dose cohort for each patient in the study.

- Once the clinical site has identified a patient for the study, before screening begins, the Investigator or his designee must complete the Pre-screening log and fax or email the form to Sunovion Pharmaceuticals Inc. or its agent.
- When a patient completes Screening, the Investigator or his designee must complete the Study Registration form and fax or email the form to Sunovion Pharmaceuticals Inc. or its agent.
- Sunovion Pharmaceuticals Inc. or its agent will provide authorization to enroll a patient by providing information regarding the appropriate dose cohort and then the clinical site will complete the Registration form to confirm assigned dose cohort and planned date of first dose and fax or email the form to Sunovion Pharmaceuticals Inc. or its agent

The Registration form will be provided as a part of the document package necessary to conduct this clinical study.

10.5.2. Selection of Dose Cohort for Each Patient

The selection of dose cohort for each patient during the dose escalation of Part 1 of the study is made based on the number of DLTs, if any, that have been observed in the current dose cohort, the number of patients enrolled in the current dose cohort, and the duration of their enrollment (eg, whether the DLT Evaluation Period is complete). After the RP2D is determined in Part 1 of the study, subsequent patients enrolled in Part 1 will initiate treatment at this dose. Selection of dose cohort for patients in Part 2 of the study is made based on the number of DLTs, if any, that have been observed in the current dose cohort, the number of patients enrolled in the current dose cohort, and the duration of their enrollment (eg, whether the DLT Evaluation Period is complete).

Upon receipt of the Study Registration form for a patient, a review of available enrollment information and occurrence of DLTs, if any, will be conducted to decide the appropriate dose cohort for the patient.

Meetings to review study execution and enrollment/dosing decisions will be held at least monthly between the sponsor, clinical sites, and the medical monitor. Instructions regarding intra-patient dose changes are described in Section 7.4.2.

10.6. Study Drug Accountability

The Investigator is responsible for storing the study drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by patients. If the study is terminated, discontinued, suspended, or completed, all unused supplies of drug will be returned to Sunovion Pharmaceuticals Inc., unless other instructions are provided in writing by Sunovion Pharmaceuticals Inc. or its agent.

The study drug will not be dispensed to any person who is not a study patient under this protocol.

10.7. Study Drug Handling and Disposal

A drug inventory record will be supplied. The Investigator on an ongoing basis must maintain a drug inventory record, using forms supplied by the Sponsor or another system that meets the requirements of Good Clinical Practice (GCP), of supplied, received, dispensed, and returned study drug. The Investigator is required to return all unused study drug to the sponsor or designee as instructed. The Investigator is required to maintain copies of study drug shipping receipts, drug accountability records, and records of return or final disposal of study drug.

11. TREATMENT PLAN

11.1. Study Assessments

11.1.1. Safety

Safety assessments will be conducted at each study visit as indicated on the Schedules of Assessments (Tables 3 - 6) and will include the spontaneous reporting of AEs, physical examinations, determinations of vital signs, body weight measurements, ECGs, and clinical laboratory determinations including complete blood count, serum chemistries, and urinalysis. Careful monitoring for signs of local injection site reactions will be performed during the study.

In addition, these assessments will be used to describe the DLT and determine the MTD. The definition of DLT is provided in Section 7.2.1 and the determination of MTD is discussed in Section 7.3.

11.1.2. Efficacy

Tumor response will be evaluated according to the irRC (Wolchok-2009, Hoos-2010), modified IWG based on Cheson-2003, and/or tumor markers, as appropriate for the diagnosis. An evaluable patient for response is defined as a patient who has had at least one tumor assessment conducted 8 weeks after the first dose of study drug or a patient who has progressive disease prior to this time point.

Survival also will be assessed.

11.1.2.1. Immune-related Response Criteria (irRC)

The irRC was chosen because immunotherapeutic agents produce antitumor effects by inducing an immune response specific to cancer cells or by modifying native immune processes that can result in clinical response after an initial increase in tumor burden or the appearance of new lesions, which is unique from cytotoxic agents.

The use of radiographic procedures, physical examinations, and measurement of tumor markers for evaluation of response will be performed based on the presence of known areas of disease and current symptoms. Unless there are compelling reasons otherwise, the tumor assessments during the study will be conducted under the same conditions (eg, slice thickness, use of a contrast agent, etc) and using the same examination method (eg, CT, MRI) as used for the pretreatment assessment.

Tumor assessments will be conducted during screening, and then every 8 weeks after the first dose of study drug, unless clinical indications require more frequent assessment. Tumor assessments are first conducted after 8 weeks to allow adequate time for immune activation and consequent antitumor responses. All tumor assessments performed on the day of study drug administration must be completed before study drug is administered.

Tumor response is based on total measurable tumor burden. For the irRC, index and measurable new lesions are taken into account. A measurable lesion is defined as 5 × 5 mm or more on helical CT scan.

At the pretreatment tumor assessment, the sum of the products of the 2 largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions, and 5 cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 × 5 mm; up to 5 new lesions per organ; 5 new cutaneous lesions; and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Percentage changes in tumor burden per assessment time point describe the size and growth of both baseline and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out immune-related progressive disease [irPD]). Decreases in tumor burden must be assessed relative to pretreatment measurements (ie, the SPD of all index lesions at screening).

Overall response will be determined by the investigator according to the irRC response assessments based on tumor burden as follows:

- irCR (immune-related complete response) = complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment 6 weeks after the date of first documentation
- irPR (immune-related partial response) = decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment 6 weeks after the date of first documentation
- irSD (immune-related stable disease) = not meeting criteria for irCR or irPR and the absence of irPD
- irPD (immune-related progressive disease) = increase in tumor burden ≥ 25% relative to nadir (prior minimum recorded tumor burden during the study) confirmation by a repeat, consecutive assessment at least 4 weeks after the date of first documentation

Note: For patients with glioblastoma, measurements should include enhancing tumor only, nonenhancing lesions (T2/FLAIR) should be recorded as improved, stable, or significant increase.

Note: For patients with glioblastoma, progressive disease should additionally be confirmed by single-photon emission computed tomography (SPECT), perfusion MRI, MRI spectroscopy or C-14 methionine positron-emission tomography (PET) or pathology from available surgical/biopsy specimens to differentiate from pseudoprogression. For patients with ovarian cancer that express CA-125, progressive disease should additionally be confirmed by CA-125 (≥ 2x higher of ULN or on study nadir).

Note: For irPD confirmation, follow-up with observation alone (during the weeks before confirmation) may not be appropriate for patients with a rapid decline in ECOG performance status or other signs of rapid clinical deterioration. The investigator should use his best judgment in determining if sooner tumor assessment is required in these patients.

Note: Patients with progressive disease based on tumor assessments who are experiencing clinical benefit in the investigator's opinion may continue on study and undergo repeat tumor

assessments. If subsequent stabilization or improvement is observed the patient may continue in the study.

11.1.2.2. Modified International Working Group response criteria in acute myeloid leukemia (IWG)

The modified International Working Group (IWG) response criteria were developed to assess the activity of drugs in AML. The criteria are as follows:

- Complete remission (CR):
  - Morphologic CR

    < 5% Marrow blasts in an aspirate with spicules – patient independent of transfusions

    Absolute neutrophil count > 1000/μL

    Platelets > 100,000/μL

    No residual evidence of extramedullary disease
  - Cytogenetic CR- cytogenetics normal (in patients with previously abnormal cytogenetics)
  - Molecular CR- molecular studies negative
- CRi - < 5% marrow blasts but with persistence of cytopenias (ie, absolute neutrophil count < 1000 /μL and/or platelets < 100,000/μL)
- Morphologic leukemia free state (MLFS) - bone marrow blasts < 5%
- Partial remission:

  Decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and the normalization of blood counts, as noted above.
- PRi:

  Decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate but with persistence of cytopenias (ie, absolute neutrophil count < 1000/μL and/or platelets < 100,000/μL).

Measurable disease will be defined as > 5% marrow blasts.

Relapse following complete remission is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause, or extramedullary relapse.

Progressive disease will be defined as increase of at least 50% in the percentage of blasts in the bone marrow aspirate with an increase of at least 10 percent of blasts in the bone marrow aspirate.

11.1.2.3. Tumor Markers

Tumor markers may be utilized to assess response as appropriate for the diagnosis. This should include at least quantitative RT-PCR for WT1 transcript in blood or bone marrow for patients

with AML, and serum CA-125 for patients with ovarian carcinoma. Measurable disease may be determined by markers alone as defined by individual laboratory normal ranges. Response will be quantified by the fractional decrease on treatment. Tumor markers drawn from peripheral blood samples should be assessed at least every 4 weeks after the first dose but may be performed more frequently.

11.1.3. Other

Biomarker analyses will be conducted as indicated on the Schedules of Assessments (Tables 3 - 6). An evaluable patient for biomarkers is defined as a patient who has had the Day 29 biomarker assessments completed. Directions for the handling and processing of biomarker samples are provided in a separate manual.

Peripheral blood samples will be obtained for evaluation of WT1 peptide-specific CTL induction activity by tetramer assay, and WT1 serum antibody titer by enzyme-linked immunosorbent assay [ELISA], and for isolation of peripheral blood mononuclear cells (PBMCs) for exploratory biomarker analyses. In addition, blood samples will be obtained and blood serum archived for possible analyses of other biomarkers, such as protein and microRNA, that may be important to the understanding of WT2725 but which have not yet been selected. Providing informed consent for use of this sample for pharmacogenetic purposes is optional, and participation in the study is not dependent upon providing this sample.

Delayed-type hypersensitivity to the WT2725 peptide will be measured approximately 48 hours (but no sooner than 24 hours) after id inoculation with WT2725 in diluted WT2725 Injection for DTH skin tests. The site of diluted WT2725 Injection inoculation will be compared to the site of inoculation with the negative control (DSWI). The criteria for evaluation include injection site erythema diameter and quality (eg, redness, induration, ulceration, etc). Directions for conducting and evaluating DTH skin tests are provided in Appendix VII.

Immunohistochemistry in tumor tissue will be evaluated by expression of CD8+, Foxp3, HLA class I, and WT1 protein using tumor tissue samples obtained before the first dose and after the last dose of study drug. In place of tumor tissue samples from biopsy during screening, archived tumor tissue samples may be provided. Biopsy for tumor tissue samples after the last dose of study drug is not mandatory and refusal to consent to post-treatment biopsy samples will not exclude a patient from enrollment in the study. IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.

11.2. Standardization of Data Capture

Study Schematic and Schedule of Assessments: For Part 1 of the study a schematic of the study design is presented in Figure 1 and a summary of assessments to be conducted at each visit are presented in Table 3, Schedule of Assessments for Screening and Vaccine Induction Phase and Table 4, Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study. For Part 2 of the study a schematic of the study design is presented in Figure 2 and a summary of assessments to be conducted at each visit are presented in Table 5, Schedule of Assessments for Screening and Vaccine Induction Phase and Table 6, Schedule of Assessments for Consolidation Phase, Maintenance Phase, and End of Study.

Vital Signs: Vital signs following 5 minutes of seated rest, will consist of supine systolic and diastolic blood pressures, respiration rate, pulse, and oral body temperature. If possible, the same arm should be used during each assessment of blood pressure and pulse throughout the study. Vital signs will be obtained prior to collection of clinical laboratory samples and performance of an ECG.

Weight and height: Weight and height should be measured in street clothing with no shoes.

Centrally-read ECG: All ECGs will be obtained in the supine position, after the patient has been resting supine for at least 10 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual patients. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. Refer to Appendix I for additional information.

Clinical Laboratory: For detailed instructions regarding laboratory procedures, sampling, and shipping guidelines refer to the site and local laboratory guidelines. Samples will be processed at a local laboratory. All laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified. See Appendix IV for a list of required clinical laboratory tests.

Adverse Events: As a discussion guide, patients should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Appendix VIII for definitions used in reporting AEs.

Concomitant Medications and Medical History: Patient self-report will be acceptable for listing all concomitant medication use, medical history, and evaluation for inclusion/exclusion except where specific protocol procedures are mandated to ensure appropriate enrollment (eg, certain baseline lab values).

11.3. Electronic Data Capture (EDC)

The study sites will use a validated EDC system to enter patient data onto case report forms (CRFs). The Data Labs system will be used for this clinical study. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

11.4. Study Visits and Assessments

11.4.1. Screening – Part 1 and Part 2

Patients will be evaluated during screening to determine their eligibility to enroll in the study. All assessments must be completed within the specified timeframes prior to the planned first dose of study drug.

11.4.1.1. Screening (within 21 days before the first dose)

The following study-related procedures will be performed

- Obtain signed informed consent and privacy authorization from the patient or his or her legal representatives before conducting any other visit procedures.
- Record all concomitant medications, including prior antineoplastic therapy, over-the counter (OTC) and health and dietary supplements taken within the previous 30 days.
- Begin recording AEs
- Review inclusion and exclusion criteria.
- Obtain medical history including demographic information.
- Obtain blood samples for hepatitis B and C, HIV-1 and HIV-2, HLA typing (if necessary), and for females of child bearing potential, for pregnancy test. *Note: HLA typing previously obtained is acceptable, otherwise HLA typing should be the first procedure performed.*
- Perform tumor assessments for baseline. Note: Results obtained within the 28 days prior to the planned first dose of study drug are acceptable (There are no variations allowed beyond this window.). If multiple assessments are available, the most recent ones should be used as the baseline result. Data from at least one additional historical assessment prior to the baseline assessment should also be provided, if available.

11.4.1.2. Screening (within 7 days before the first dose)

The following study-related procedures will be performed

- Perform physical examination.
- Obtain vital signs (systolic and diastolic blood pressures, pulse, respiration rate, and oral body temperature) including height and weight.
- Obtain ECOG Performance Status.
- Perform 12-lead ECG.
- Obtain urine sample for urinalysis.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood sample for CTL induction activity.
- Obtain tumor samples for IHC. In place of tumor tissue samples obtained from a biopsy during screening, archived tumor tissue samples may be provided. Availability of tumor tissue samples should be determined during screening through provision of the accession number or other identification number. If necessary, the tumor tissue sample biopsy should be performed after study eligibility has been confirmed and before the first administration of study drug. The tumor tissues samples will only be provided to the sponsor for patients who receive study drug. Instructions for tissue sample processing and shipment are provided in a separate manual. In place of archival tumor tissue samples, patients with AML should have available a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. Patients with AML should also have peripheral

blood assessed for blasts and WT1 transcript. IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.

- Record AEs and concomitant therapies as necessary.
- Review inclusion and exclusion criteria.

11.4.2. Study Treatment Periods

11.4.2.1. Vaccine Induction Phase – Part 1

During the vaccine induction phase, patients will receive study drug once every 7 days for 4 weeks, ie, a total of 5 doses. Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.1).

11.4.2.1.1. Day -2

Approximately 48 hours (but no sooner than 24 hours) before planned first dose:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.1.2. First Dose (Day 1 [-1])

Day 1

- Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG. *Note: May be omitted if performed within the previous 3 days. If multiple assessments are available, the most recent ones should be used.*
- Obtain blood samples for hematology and serum chemistry and for females of child-bearing potential, for pregnancy test. *Note: May be omitted if performed within the previous 3 days. If multiple assessments are available, the most recent ones should be used.*
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, PBMC isolation, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis. *Note: May be omitted if performed within the previous 3 days. If multiple assessments are available, the most recent ones should be used.*
- Review continuation criteria.
- Perform evaluation of DTH skin test.

- Perform injections for new DTH skin test immediately before administration of study drug.

Administer study drug.

6 hours (± 30 minutes) postdose

- Obtain blood sample for retrospective biomarker analyses.

11.4.2.1.3. Day 3

Approximately 48 hours (±6 hours) after the dose on Day 1:

- Obtain blood sample for retrospective biomarker analyses.
- Record AEs and concomitant therapies as necessary.

Perform evaluation of DTH skin test, approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injections on Day 1.

11.4.2.1.4. Second Dose (Day 8 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity and retrospective biomarker analyses.
- Review continuation criteria.

Administer study drug.

11.4.2.1.5. Third Dose (Day 15 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis.

- Review continuation criteria.

Administer study drug.

11.4.2.1.6. Fourth Dose (Day 22 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Review continuation criteria.

Administer study drug.

11.4.2.1.7. Day 27

Approximately 48 hours (but no sooner than 24 hours) before planned fifth dose:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.1.8. Fifth Dose (Day 29 [-1])

Day 29

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, PBMC isolation, retrospective biomarker analyses, and tumor markers drawn from peripheral blood.
- Obtain urine sample for urinalysis.
- Review continuation criteria.
- Perform evaluation of DTH skin test.

- Perform injections for new DTH skin test immediately before administration of study drug.

Administer study drug.

11.4.2.1.9. Day 31

Approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injections on Day 29:

- Record AEs and concomitant therapies as necessary.
- Perform evaluation of DTH skin test.

11.4.2.2. Consolidation Phase – Part 1

During the consolidation phase, patients will receive study drug once every 14 days for 6 weeks, ie, a total of 4 doses. Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.1).

11.4.2.2.1. Sixth Dose (Day 43 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood sample for CTL induction activity.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.2.2. Seventh Dose (Day 57 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.

- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis.

- Perform tumor assessments for response. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least every 4 weeks after the first dose. Other tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the first dose. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug.
- Review continuation criteria.

Administer study drug.

11.4.2.2.3. Eighth Dose (Day 71 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood sample for CTL induction activity.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.2.4. Day 83

Approximately 48 hours (but no sooner than 24 hours) before planned ninth dose:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.2.5. Ninth Dose (Day 85 [± 2])

Day 85

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.

- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, retrospective biomarker analyses, and tumor markers drawn from peripheral blood.
- Obtain urine sample for urinalysis.
- Perform evaluation of DTH skin test. Review continuation criteria.
- Perform injections for new DTH skin test immediately before administration of study drug.

Administer study drug.

11.4.2.2.6. Day 87

Approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injections on Day 85:

- Record AEs and concomitant therapies as necessary.
- Perform evaluation of DTH skin test.

11.4.2.3. Maintenance Phase – Part 1

During the maintenance phase, patients will receive study drug once every 28 days until discontinuation. Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.1).

During each dosing day the following assessments will be performed as noted.

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Obtain blood samples for WT1 serum antibody titer and retrospective biomarker analyses every second dosing day after the ninth dose.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

- Perform tumor assessments for response every 8 weeks after the first dose or more frequently as clinically indicated. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least every 4 weeks after the first dose. Other tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the first dose. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug.

Administer study drug.

11.4.2.4. Vaccine Induction Phase – Part 2

During the vaccine induction phase, patients will receive study drug once every 7 days for 8 weeks, ie, a total of 9 doses. Additional dosing windows are provided in Section 8.3.2.2.

11.4.2.4.1. Day -2

Approximately 48 hours (but no sooner than 24 hours) before planned first dose:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.4.2. First Dose (Day 1 [-1])

Day 1

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG. *Note: May be omitted if performed within the previous 3 days. If multiple assessments are available, the most recent ones should be used.*
- Obtain blood samples for hematology and serum chemistry and for females of child-bearing potential, for pregnancy test. *Note: May be omitted if performed within the previous 3 days. If multiple assessments are available, the most recent ones should be used.*
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, PBMC isolation, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis. *Note: May be omitted if performed within the previous 3 days. If multiple assessments are available, the most recent ones should be used.*
- Review continuation criteria.

- Perform evaluation of DTH skin test.
- Perform injections for new DTH skin test immediately before administration of study drug.

Administer study drug.

6 hours (± 30 minutes) postdose

- Obtain blood sample for retrospective biomarker analyses.

11.4.2.4.3. Day 3

Approximately 48 hours (±6 hours) after the dose on Day 1:

- Obtain blood sample for retrospective biomarker analyses.
- Record AEs and concomitant therapies as necessary.

Perform evaluation of DTH skin test, approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injections on Day 1.

11.4.2.4.4. Second Dose (Day 8 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity and retrospective biomarker analyses.
- Review continuation criteria.

Administer study drug.

11.4.2.4.5. Third Dose (Day 15 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, and retrospective biomarker analyses.

- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.4.6. Fourth Dose (Day 22 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Review continuation criteria.

Administer study drug.

11.4.2.4.7. Day 27

Approximately 48 hours (but no sooner than 24 hours) before planned fifth dose:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.4.8. Fifth Dose (Day 29 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, PBMC isolation, retrospective biomarker analyses, and tumor markers drawn from peripheral blood.
- Obtain urine sample for urinalysis.
- Review continuation criteria.
- Perform evaluation of DTH skin test.

- Perform injections for new DTH skin test immediately before administration of study drug.

Administer study drug.

11.4.2.4.9. Day 31

Approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injections on Day 29:

- Record AEs and concomitant therapies as necessary.
- Perform evaluation of DTH skin test.

11.4.2.4.10. Sixth Dose (Day 36 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Review continuation criteria.

Administer study drug.

11.4.2.4.11. Seventh Dose (Day 43 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood sample for CTL induction activity.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.4.12. Eighth Dose (Day 50 [-1])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Review continuation criteria.

Administer study drug.

11.4.2.4.13. Ninth Dose (Day 57 [-1)]

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis.
- Perform tumor assessments for response. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least every 4 weeks after the first dose but may be performed more frequently. Other tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the first dose or more frequently a clinically indicated. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug.
- Review continuation criteria.

Administer study drug.

11.4.2.5. Consolidation Phase Part 2

During the consolidation phase, patients will receive study drug once every 14 days for 10 weeks (maximum 6 doses). Additional dosing windows are provided in Section 8.3.2.2.

11.4.2.5.1. Tenth Dose (Day 71 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood sample for CTL induction activity.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.5.2. Day 83

Approximately 48 hours (but no sooner than 24 hours) before planned ninth dose:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.5.3. Eleventh Dose (Day 85 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, retrospective biomarker analyses, and tumor markers drawn from peripheral blood.
- Obtain urine sample for urinalysis.
- Perform evaluation of DTH skin test.
- Review continuation criteria.
- Perform injections for new DTH skin test immediately before administration of study drug.

Administer study drug.

11.4.2.5.4. Day 87

Approximately 48 hours (but no sooner than 24 hours) after the DTH skin test injections on Day 85:

- Record AEs and concomitant therapies as necessary.
- Perform evaluation of DTH skin test.

11.4.2.5.5. Twelfth Dose (Day 99 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.5.6. Thirteenth Dose (Day 113 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis.
- Perform tumor assessments for response. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least every 4 weeks after the first dose but may be performed more frequently. Other tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the first dose or more frequently a clinically indicated. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug.
- Review continuation criteria.

Administer study drug.

11.4.2.5.7. Fourteenth Dose (Day 127 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.5.8. Fifteenth Dose (Day 141 [± 2])

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, retrospective biomarker analyses, and tumor markers drawn from peripheral blood.
- Obtain urine sample for urinalysis.
- Review continuation criteria.

Administer study drug.

11.4.2.6. Maintenance Phase – Part 2

During the maintenance phase, patients will receive study drug once every 28 days until discontinuation. Additional dosing windows are provided for patients who may need to recover from intercurrent medical conditions (see Section 8.3.2.2).

During each dosing day the following assessments will be performed as noted.

Record AEs and concomitant therapies as necessary.

Predose

- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry.
- Obtain blood samples for CTL induction activity.
- Obtain blood samples for WT1 serum antibody titer and retrospective biomarker analyses every second dosing day after the start of the maintenance phase (monthly dosing schedule).
- Obtain urine sample for urinalysis.
- Review continuation criteria.
- Perform tumor assessments for response every 8 weeks after the first dose or more frequently as clinically indicated. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated or per the post-transplant schedule/institutional policy if no other indicator of measurable disease, however peripheral blood should be assessed for blasts and WT1 transcript at least every 4 weeks after the first dose but may be performed more frequently. Other tumor markers drawn from peripheral blood samples should be assessed every 4 weeks after the first dose or more frequently as clinically indicated. This assessment may be performed ± 7 days of the scheduled assessment but must be completed before the next planned administration of study drug.

Administer study drug.

11.4.2.7. 48 hours Before End of Study Evaluations – Part 1 and Part 2

Approximately 48 hours (but no sooner than 24 hours) before planned End of Study visit:

- Perform injections for DTH skin test.
- Record AEs and concomitant therapies as necessary.

11.4.2.8. End of Study (EOS) (within 28 days after last dose of study drug and prior to start of alternate antineoplastic therapy) – Part 1 and Part 2

All patients should complete an End of Study visit within 28 days after the last dose of study drug and prior to the start of alternate antineoplastic therapy. During the End of Study visit, the following assessments will be performed.

- Record AEs and concomitant therapies as necessary.
- Obtain ECOG Performance Status.
- Perform physical examination.
- Obtain vital signs and weight.

- Perform 12-lead ECG.
- Obtain blood samples for hematology and serum chemistry, and for females of child-bearing potential, for pregnancy test.
- Obtain blood samples for CTL induction activity, WT1 serum antibody titer, PBMC isolation, and retrospective biomarker analyses.
- Obtain urine sample for urinalysis.
- Perform evaluation of DTH skin test.
- Obtain tumor samples for IHC from all patients who provided consent.
- Perform tumor assessments for response. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood should be assessed for blasts and WT1 transcript at least at every scheduled tumor assessment.
- Assess disease progression and survival.

11.4.3. Follow-up – Part 1 and Part 2

Following the End of Study visit, patients will be contacted every 3 months until the study is closed to evaluate disease progression, if not already reached, and survival.

12. DISCONTINUATION AND REPLACEMENT OF PATIENTS/ CLINICAL ASSESSMENTS AFTER STUDY MEDICATION DISCONTINUATION

12.1. Clinical Assessments After Study Medication Discontinuation

Every effort should be made for all treated patients discontinuing study drug, regardless of cause, and, prior to the start of alternate treatment to undergo final evaluation procedures, in accordance with the End of Study visit as described in Section 11.4.2.8.

12.2. Study Participation Termination Criteria

The possible reasons for study drug discontinuation and study participation termination are to be assessed for each enrolled patient and are as follows:

- Adverse event.
- Progressive disease.
- Death:
    - Death due to progressive disease.
    - Death due to other causes
- Study stopped by sponsor.
- Lost to follow-up.
- Protocol violation (specify).
- Pregnancy.
- Withdrawal by patient (specify).
- Other (specify).

12.3. Replacement of Patients

Patients who discontinue from the study for a reason other than DLT prior to completing the DLT Evaluation Period will be replaced.

13. ADVERSE EXPERIENCE REPORTING

13.1. Adverse Events

An AE is any new, untoward medical occurrence or worsening of a pre-existing medical condition that occurs during study participation, whether or not the event is considered drug related.

AEs will be collected from the time the informed consent is signed through the end of the study. Serious adverse events will be collected and reported on the SAE form, from the time of informed consent through 30 days post last dose and will be followed until resolution or lost to follow-up. SAEs occurring from the time of informed consent through the end of study must be recorded on the CRF and the data recorded should match that on the SAE form.

Non-leading questions will be used to ask patients about the possible occurrence of AEs. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

Following questioning and evaluation, all AEs, whether believed by the Investigator to be related or unrelated to the study drug, must be documented in the patient's study records/source documents, in accordance with the Investigator's normal clinical practice, and on the AE page of the CRF. Each AE is to be evaluated for duration, severity according to the CTCAE V.4.0, seriousness, and causal relationship to the study medication. Appendix VIII (Definitions for Reporting Adverse Events) provides definitions for relationship to study medication, and action taken, and reference to CTCAE for grade. An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the experience may have been caused by the drug" (21 CFR 312.32 [a]).

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found on page 3 of this protocol.

13.2. Objective Findings

New and worsening signs and symptoms of underlying or emerging disease must be recorded as AEs. Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded on the Adverse Event page of the CRF from signing of the informed consent onwards. When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) will be recorded as the AE.

Progression of the malignancy being treated in the study is not reported as an AE. Hospitalization due solely to progression of the malignancy being treated in the study is not an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be

determined as exclusively due to the malignancy being treated in the study, or if they do not fit the expected pattern of progression for the malignancy being treated in the study.

Clinical laboratory test results will be reviewed by an Investigator as they become available. Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. Laboratory reports, as appropriate when an electronic medical records system is not used, will be initialed and dated on all pages by a Form FDA 1572-listed Investigator.

All on-site ECG tracings and ECG over-read reports will be reviewed by an Investigator as they become available. The Investigator must determine the clinical significance of all abnormal ECG interpretations on the machine read tracing. Possibly drug-related or clinically relevant abnormal ECGs of uncertain causality must be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings, as necessary when an electronic system is not used, will be initialed and dated on all pages by a Form FDA 1572-listed Investigator.

13.3. Immediately Reportable Events

There are 2 categories of medical events that could occur during participation in a clinical study that must be immediately reported to Sunovion Pharmaceuticals Inc. or its agent:

- SAE, including death.
- The incidence of pregnancy.

PPD Pharmacovigilance (PVG) must be contacted immediately upon first knowledge of the incident.

PPD PVG:

Phone hotline: (919) 456-6001

Fax: (919) 654-0211

Email: Sunovionsafety@druginfo.com

Emergency contact information can also be found on page 3 of this protocol.

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, in-patient hospitalization or prolongation of existing hospitalization (Hospitalization due solely to progression of the malignancy being treated in the study is not an SAE.), a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening means that the patient was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form might have caused death.

If an Investigator or study site staff becomes aware of a SAE that occurs in a study patient from the time that informed consent is signed through 30 days following the last dose of study medication, this must be reported immediately to PPD PVG.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and sent via fax to PPD PVG within 1 business day of an Investigator or study site staff becoming aware of the event. Sunovion Pharmaceuticals Inc. provides the SAE form used to report SAEs as a part of the document package necessary to conduct this clinical study.

Sunovion Pharmaceuticals Inc. will promptly notify all research sites of an AE that is determined to be reportable to the Regulatory Authorities. These AEs must be promptly reported to the Institutional Review Board (IRB) by the Principal Investigator.

If a patient becomes pregnant during the course of the study, she will be instructed to immediately stop taking study medication. Further, the patient will be instructed to return within 48 hours of the first notification of pregnancy to the research site and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the patient will no longer receive any additional study medication and will continue to be followed. All pregnancies, whether or not the patient received any study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

To report a pregnancy, the Pregnancy Event Form must be completed and sent via facsimile to PPD PVG within 1 business day of first knowledge by the research personnel of the pregnancy. Sunovion Pharmaceuticals Inc. provides the Pregnancy Event Form as a part of the document package necessary to conduct this clinical study. Pregnancies occurring from the time the informed consent is signed through 30 days following the last dose of study medication will be followed quarterly until birth or termination of the pregnancy.

If a pregnancy is reported for a male study patient’s partner, the Sponsor’s representative will provide instructions on how to collect pregnancy information in accordance with local requirements. Proper consent to collect the partner’s information will be obtained prior to the collection of any information.

14. STATISTICS

14.1. Sample Size Determination

The sample size for Part 1 and Part 2 is based on clinical and practical considerations for a Phase 1 dose escalation study using the rolling-six design and is outside of statistical considerations.

14.2. Randomization and Blinding

No randomization or blinding will be employed, open-label study drug will be used and there is no comparator.

14.3. Unblinding Procedures

Not applicable for this study. All study drug will be open label.

14.4. Analysis Populations

There are 3 planned analysis populations for this study.

The Safety population will include all enrolled patients who receive at least 1 dose of study drug and will be used for the analysis of all safety and efficacy data except as noted below.

If needed, a DLT population will include all patients in the Safety population who are evaluable for DLT evaluation and will be used for analysis of DLT.

If needed, an Efficacy population will include all patients in the Safety population who are evaluable for response and will be used for analysis of response assessment.

14.5. Data Analysis

Data will generally be summarized by enrolled or starting dose, unless otherwise indicated. Efficacy data may also be summarized by tumor type and/or outcome measure. Descriptive statistics including number of patients, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum will be provided.

No imputation will be performed for missing data in this Phase 1 study.

14.5.1. Patient Disposition

The number and percentage of patients will be presented by dose cohort, together, with the number and percentage of patients who withdrew from the study for each study discontinuation reason. Reason for discontinuation for all patients will be listed by dose cohort.

14.5.2. Drug Exposure and Compliance

Study drug exposure including cumulative dose and duration of exposure will be summarized by dose cohort. Duration of exposure (ie, weeks on study drug) will be calculated as the number of weeks from first to last dose date. The number of patients with a dose reduction, dose escalation, and no dose modification in each enrolled dose cohort will also be summarized. All patients will

be administered study drug in clinic, and all recorded exposure or compliance information will listed by patient.

14.5.3. Important Protocol Deviations

Important Protocol Deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potential IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potential IPDs to be reviewed include, but are not limited to, patients who:

- Did not meet inclusion/exclusion or continuation criteria
- Received any disallowed concomitant medication or therapy

The number of patients with each type of IPD will be tabulated by category and by deviation type for all patients in the Safety population by dose cohort. Individual IPDs will be presented in a data listing.

14.5.4. Demographic and Baseline Characteristics

The number of patients of each sex, in each racial group, in each ethnicity group, and in each ECOG performance status score category will be summarized. Age and body mass index (BMI) will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum).

The medical history of patients will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0 or higher. The number of patients with abnormal findings in each SOC and each PT will be summarized. Cancer history also will be summarized.

14.5.5. Efficacy Analysis

Tumor response category evaluated according to the irRC, modified IWG, and/or tumor markers will be summarized by dose cohort, and will be listed for each patient. Response assessments for the irRC, modified IWG, and/or tumor markers will be summarized separately. The number of patients in each overall response category will be provided. Descriptive statistics will similarly be provided for the percent change from baseline in tumor burden where applicable.

The distribution of biomarker values will be summarized at each time point and at the last assessment by dose cohort using descriptive statistics, and data will be listed for each patient.

The relationship between the level of expression of WT1 protein and the degree of immune response as measured by CTL induction will be assessed graphically and the Spearman rank correlation coefficient will be estimated.

14.5.6. Adjustment for Multiplicity

No adjustment for multiple comparisons will be used as no statistical testing is planned and all analyses are considered exploratory in nature.

14.5.7. Safety Analysis

Safety measures will be summarized using descriptive statistics generally by enrolled dose cohort and listed for each patient.

14.5.7.1. DLT and Adverse Events

All AEs will be coded using MedDRA, version 14.0 or higher.

The occurrence of DLT events during the DLT evaluation period will be summarized for each dose cohort.

Treatment-emergent adverse events (TEAEs) will be defined as:

- AEs that occurred on or after the first dose of study drug and on or before the 30th day after the last dose of study drug,
- AEs with a missing start date and a stop date on or after the first dose of study drug, or
- AEs with both a missing start and stop date.

TEAEs will be summarized by dose cohort and overall and by MedDRA SOC and PT.

The following AEs will be summarized and presented by enrolled dose cohort and by MedDRA SOC and PT for the Safety population:

- All TEAEs (including number of events and patient incidence)
- TEAEs by relationship to treatment (unrelated, or related)
- TEAEs by CTCAE Grade

Similar summaries will be presented by the last dose received before the start of the event.

The following conventions will be followed in summarizing AEs:

- For patient incidence summaries, each patient will be counted only once within each SOC and within each PT.
- If a patient reports more than one AE within a PT and/or a SOC, the AE with the highest known grade within each SOC and within each PT will be included in the summaries by grade.
- For summaries by relationship to study medication, AEs whose relationship to treatment is assessed as “not related” will be grouped as “unrelated.” AEs assessed as “possible,” “probable,” or “definite,” unknown or missing will be grouped as “related.” If a patient reports more than one AE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related.

A listing of all TEAEs, SAEs, and AEs leading to discontinuation or death, will be presented. A separate listing for non-treatment-emergent AEs will also be provided.

14.5.7.2. Clinical Laboratory Assessments

For laboratory parameters with continuous outcomes, descriptive statistics will be presented for each dose cohort and within each tumor group at each time point. Changes from baseline will be

summarized in the same manner. For laboratory parameters with categorical outcomes, the number of patients with each outcome will be presented. The data listings for laboratory parameters will flag values outside of the reference range.

14.5.7.3. Electrocardiograms

A standard 12-lead ECG will be used to collect and record electrocardiographic data according to the schedule of assessments. Parameters to be collected include ventricular heart rate, QT interval, PR interval, QRS duration, and RR interval (ms). The corrected QT interval will be derived according to the Fridericia formula ($QT_{c-F} = QT/[R\text{-}R/1000]^{1/3}$) as well as Bazett's formula ($QT_{c-B} = QT/[R\text{-}R/1000]^{1/2}$).

ECG parameters and changes in these parameters from predose Day 1, as determined by the central over-read, will be summarized using descriptive statistics at each time point by dose cohort.

The number of patients with QT_{c-F} values in the following categories will be summarized:

- $QT_{c-F} \geq 500$ ms at any postdose time point and not present at baseline
- $QT_{c-F} \geq 450$ ms at any postdose time point and not present at baseline
- Change from baseline in $QT_{c-F} \geq 60$ ms for at least 1 postdose measurement
- Change from baseline in $QT_{c-F} \geq 30$ ms for at least 1 postdose measurement, but < 60 ms for all postdose measurements

Any unscheduled ECG that occurs after first dose will be included for these post-treatment summaries.

The above categorical analyses will also be performed for QT_{c-B}.

A listing of patients with over-read ECG abnormalities including overall, rhythm, conduction, morphology, myocardial infarction, and the presence of ST, T, and U wave abnormalities will be presented.

14.5.7.4. Vital Signs

Body temperature, respiration rate, pulse, blood pressure (diastolic and systolic), and weight will be summarized using descriptive statistics at each time point by dose cohort. Changes from baseline will be summarized in the same manner.

14.5.7.5. Physical Examination

Findings from the physical examinations will be presented as follows: pre-existing clinically significant conditions recorded as medical history will be summarized as described in Section 14.5.4, any new clinically significant conditions recorded as AEs will be summarized as described in Section 14.5.7.1.

14.5.7.6. Concomitant Medications

Other than the study drug, any medication taken by patients during the course of the study with a start date or an end date on or after the date of the first dose of study drug, or marked as ongoing, will be considered concomitant. Medications stopped prior to the date of the first dose of study

drug will not be considered concomitant. The number of patients using each concomitant medication will be summarized for each treatment according to the World Health Organization Drug Dictionary (WHODRUG) Anatomic Therapeutic Class (ATC) class and PT. Patients with multiple uses of a concomitant medication during a treatment period will be counted once for a given ATC and PT for the treatment period.

14.5.8. Treatment of Missing Data

For analyses of change from baseline, baseline will generally be defined as the predose assessment on Day 1 or during screening as scheduled. If this value is unavailable, the last non-missing value prior to the first dose of study drug will be used. Otherwise, missing observations will be treated as missing at random, and no data imputation will be performed.

15. COMPUTERIZED SYSTEMS USED FOR SOURCE DATA

A list of the computerized systems that will be used at each step to create, modify, maintain, archive, retrieve, or transmit source data are presented below, per the *Guidance for Industry Computerized Systems Used in Clinical Investigations*, May 2007.

Table 7: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Informed Consent	NA
Inclusion/Exclusion Review	A
Continuation Criteria	A
Study Drug Administration	A
Medical History	A
Physical Exam	A
Height	A
Weight	A
Vital Signs	A
ECOG performance status	A
HLA typing	B
FSH testing	A
Serum Pregnancy Test	A
Serology	A
Hematology/Serum Chemistry	A
Urinalysis	A
12-Lead ECG	C
DTH Skin Test	B
Blood Sample for CTL	B
Blood Sample for Anti-WT1 Antibody	B
Blood Sample for PBMC isolation	B
Blood Sample for Retrospective Biomarker Analysis	B
IHC Tumor Samples	A
Tumor Assessment	A
Adverse Events	A
Concomitant Medications	A
Disease Progression/ Survival	A
Statistical Analysis	SAS®, version 9.1.3 or higher

Abbreviations: CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EDC = electronic data capture, FSH = follicle-stimulating hormone, HLA = human leukocyte antigen, IHC = immunohistochemistry, LIMS = laboratory information management system, NA = not applicable, PBMC = peripheral blood mononuclear cells, WT1 = Wilms' tumor gene product 1

Note: A = EDC (PRA International); B = LIMS/ASCII; C = Core Lab Over-read

16. ETHICAL AND REGULATORY OBLIGATIONS

16.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, the US Code of Federal Regulations (CFR), GCP (E6), and the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and current audits, and will demonstrate due diligence in recruiting and screening study patients.

The Investigator must sign and return to Contract Research Organization (CRO)/Sponsor the "Study Acknowledgment" page and provide a copy of current curriculum vitae (CV), including a copy of a current medical license, and financial disclosure.

For all studies conducted under an Investigational New Drug (IND), the Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to CRO/Sponsor.

16.2. Institutional Review Board or Independent Ethics Committee

Before initiation of the study, the Investigator/CRO must obtain approval or favorable opinion of the research protocol, informed consent form, and any advertisement for patient recruitment, from an IRB or Independent Ethics Committee (IEC) complying with the provisions specified in 21 CFR Part 56 or in ICH GCP, as applicable, and applicable pertinent government regulations. The Investigator must assure IRB or IEC compliance with the applicable regulations.

A copy of written IRB or IEC approval or favorable opinion of the protocol, informed consent form and advertising (if applicable) must be provided to CRO/Sponsor prior to initiation of the study. The approval or favorable opinion letter must be signed by the IRB or IEC chairman or designee, identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB or IEC complies with the requirements in 21 CFR Part 56 for a study conducted under an IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not exceeding one year or otherwise specified by the IRB or IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs or other safety information reported from CRO/Sponsor in accordance with 21 CFR 312.66, or when dictated by applicable local regulations (ie, Directive 2001/20/EC), the Sponsor/CRO is responsible for reporting to the IEC (eg, reporting of serious AEs).

16.3. Informed Consent

The Investigator will prepare the informed consent form and provide the form to CRO/Sponsor for approval prior to submission to the IRB or IEC. CRO/Sponsor may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by the FDA or governing regulatory authority and ICH guidelines and will be subject to CRO/Sponsor approval as well as IRB or IEC approval. CRO/Sponsor may submit informed consent forms to a central IRB or IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective candidate will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the individual understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each patient must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. The Investigator will provide a copy of the signed informed consent form to each patient. It should be clearly explained to each patient that participation in each and every clinical visit and assessment is expected. The patient may be discontinued from study drug, but that does not necessarily negate the expectation that the patient will continue to participate in the study through the final visit/assessment.

If an amendment to the protocol changes the patient participation schedule in scope or activity, or increases the potential risk to the patient, the informed consent form must be revised, submitted to the IRB or IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a patient currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new patients who are enrolled into the study after the date of the approval or favorable opinion of the amendment.

16.4. Patient Privacy

The Sponsor's staff or any designees affirm and uphold the patient's confidentiality. Throughout this study, all data forward to the Sponsor will be identified only by an identification number, date of birth, gender, and initials. The Investigator agrees that the Sponsor's representatives, its designee, representatives of the relevant IRB/IEC or representatives of the regulatory authorities will be allowed to review that portion of the patient's primary medical records that directly concerns this study (including, but not limited to, clinical laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a patient's study participation and autopsy reports for deaths occurring during the study).

For the studies conducted in the US, in accordance with the Healthcare Insurance, Portability, and Accountability Act of 1996, the Investigator will prepare a privacy authorization form and provide the form to CRO/Sponsor for approval prior to submission to the IRB/IEC or to a Privacy Board. CRO/Sponsor may provide a template privacy authorization form to be qualified by each research facility to conform to local requirements. The content of the privacy

authorization form must comply with the regulations governing the authorization. All prospective study candidates will be given full explanation of the privacy authorization form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the Investigator is assured that the individual understands the implications of the privacy authorization form, the patient will be asked to sign the privacy authorization. The authorization remains in effect until revoked by the patient. The Investigator will provide a copy of the signed privacy authorization form to each patient. Patients who do not sign the privacy authorization form will not be permitted to participate in the study.

16.5. Protocol Amendments and Emergency Deviations

Changes to the research covered by this protocol must be implemented by formal protocol amendment. Amendments to the protocol may be initiated by the Sponsor or at the request of the Investigator. In either case, a formal amendment cannot be initiated until the Sponsor has approved it, the Investigator has signed it off, and it has been reviewed and has received approval or favorable opinion by the IRB or IEC.

Emergency deviations or modifications may be initiated without the Sponsor's or IRB/IEC approval or favorable opinion, only in cases where the change is necessary to eliminate an immediate apparent hazard to patients. Emergency deviations or modifications must be reported to CRO/Sponsor and the IRB/IEC within five business days of the occurrence, or in accordance with applicable regulatory requirements.

The study will not be un-blinded (where applicable) until all data have been reviewed, data entry has been completed, and the database is locked.

16.6. Monitoring and Auditing of the Study

A clinical monitor, whether an employee of the Sponsor or its designated representative, has the obligation to follow this study closely. In doing so, the monitor will visit the clinical study sites at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. Quality assurance auditors, whether an employee of the Sponsor or its designated representative, may evaluate the conduct of the study by the clinical study sites. These parties must have access to any and all study-related documentation including source documentation, regardless of location and format. The Sponsor audit reports will be kept highly confidential.

16.7. Study Documentation

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation and CRFs as part of the case histories.

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment

manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source documentation is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or is in support of the protocol specifications, eg, clinical lab reports, clinic notes, drug disbursement log, patient sign in sheets, patient completed questionnaires, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed lab reports and hard copy lab reports, faxed initial results and hard copy, final report.

CRO/Sponsor will supply CRFs. All requested information must be entered on the CRFs. Every effort should be made to complete all forms in their entirety. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. Each set of completed CRFs must be reviewed, electronically signed and dated by the Investigator.

16.8. Laboratory Certification and Normal Values

A local laboratory will be used for analysis for most of the clinical labs for this study. The site personnel will provide the CRO and Sponsor with laboratory certification(s), a dated copy of normal range values for the local laboratory clinical laboratory selected to analyze clinical specimens, and the lab director's CV.

16.9. Drug Accountability

The Investigator is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by patients. If the investigation is terminated, discontinued, suspended, or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by CRO/Sponsor.

The drug will not be dispensed to any person who is not a study patient under this protocol.

16.10. Records Retention

The Investigator agrees to retain study records for the time periods stated below. The Investigator agrees to contact CRO/Sponsor before destroying any study documentation. Should the Investigator leave the site at which the study was conducted, CRO/Sponsor will be contacted regarding the disposition of document storage.

Records will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Dates marking the beginning of the final record retention periods will be sent in writing from CRO/Sponsor. If an Investigator withdraws from the study (eg, relocation), the records will be transferred to a mutually agreed upon designee (ie, another Investigator). This transfer is subject to Sponsor approval and will be documented in writing and a copy sent to the Sponsor.

Electronic Data Capture/ Electronic Patient Reported Outcomes (ePRO) Data Archiving:

In compliance with data retention requirements, and after the capture phase of the study is complete, the site will receive a copy of all eSource data and accompanying audit trail from the EDC and/or ePRO vendors. The vendors shall certify the integrity of the copy (certified copy) and send it on commonly readable storage material (CD or DVD); if necessary, software for viewing the data files and instruction on installation and use of the software will also be included. This read-only archive will be retained, protected, and made accessible by the site throughout the required retention period.

16.11. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor, its representative, the Food and Drug Administration or other regulatory authorities' access to all study records. The Investigator will promptly notify CRO/Sponsor of all requests to inspect by government agencies and will promptly forward a copy of all such inspection reports.

16.12. Financial Disclosure

Prior to the start of the study, Investigators will release sufficient and accurate financial information that permits CRO/Sponsor to demonstrate that an Investigator and all sub-Investigators listed on the Form FDA 1572, if appropriate, have no personal or professional financial incentive regarding the future approval or disapproval of the study medication such that his or her research might be biased by such incentive. Investigators will provide an update of the above financial information at the end of the study and one year following the end of the study.

17. STUDY ACKNOWLEDGMENT

I have read the foregoing protocol, D8350004, Version 7.0, "Initial Phase 1 Study of WT2725 Dosing Emulsion in Patients with Advanced Malignancies", and agree that it contains all necessary details for conducting this study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

18. REFERENCES

Buonaguro L, Petrizzo A, Tornesello ML, Buonaguro FM. Translating tumor antigens into cancer vaccines. Clin Vaccine Immunol 2011;18(1):23-34.

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendation of the international working group for the diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21:4642-9.

Eifuku R, Takenoyama M, Yoshino I, Imahayashi S, So T, Yasuda M, et al. Analysis of MAGE-3 derived synthetic peptide as a human lung cancer antigen recognized by cytotoxic T lymphocytes. Int J Clin Oncol 2001;6:34-9.

Fleischhauer K, Tanzarella S, Wallny H, Bordignon C, Traversari C. Multiple HLA-A alleles can present an immunodominant peptide of the human melanoma antigen Melan-A/MART-1 to a peptide-specific HLA-A*0201+ cytotoxic T cell line. J Immunol 1996;157:787-97.

Franko A, Magliocco AM, Duan Q, Duggan MA. WT1 Immunoprofiling and Comparison of Malignant Mullerian Mixed Tumors of The Female Genital Tract. International Journal of Gynecological Pathology 2010;29:452–8.

Gentilini C, Letsch A, Asemissen A, Muessig A, Rieger K, Scheibenbogen C, et al. Vaccination with WT-1 126-134 peptide in patients with acute myeloid leukemia after allogenic stem cell transplantation. Blood 2006;108(11):1052a-53a.

Hoos A, Eggermont AMM, Janetzi S, Hodi FS, Ibrahim R, Anderson A, et al. Improved endpoints for cancer immunotherapy trials. JNCI 2010;102(18):1388-97.

Hutchings Y, Osada T, Woo CY, Clay TM, Lyerly HK, et al. Immunotherapeutic targeting of Wilms' tumor protein. Curr Opin Mol Ther 2007;9(1):62-9.

Kaida M, Morita-Hoshi Y, Soeda A, Wakeda T, Yamaki Y, et al. Phase 1 Trial of Wilms tumor 1 (WT1) peptide vaccine and gemcitabine combination therapy in patients with advanced pancreatic or biliary tract cancer. J Immunother 2011;34(1):92-9.

Keilholz U, Letsch A, Busse A, Asemissen AM, Bauer S, et al. A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS. Blood 2009;113(26):6541-8.

Kuball J, de Boer K, Wagner E, Wattad M, Antunes E, et al. Pitfalls of vaccinations with WT1-, Proteinase3-, and MUC1-derived peptides in combination with MontanideISA51 and CpG7909. Cancer Immunol Immunoth 2011;60:161-71.

Li Z, Oka Y, Tsuboi A, Fujiki F, Harada Y, Nakajima H, et al. Identification of a WT1 protein-derived peptide, WT1, as a HLA-A 0206-restricted, WT1-specific CTL epitope. Microbiol Immunol 2008; 52:551-8,

Maslak PG, Dao T, Krug LM, Chanel S, Korontsvit T, et al. Vaccination with synthetic analog peptides derived from WT1 oncoprotein induces T-cell responses in patients with complete remission from acute myeloid leukemia. Blood 2010;116(2):171-9.

Nakatsuka S, Oji Y, Horiuchi T, Kanda T, Kitagawa M, et al. Immunohistochemical detection of WT1 protein in a variety of cancer cells. Modern Pathology 2006;19:804-14.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events v4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. NIH publication # 09-7473. Published 29 May 2009. Accessed 17 Jan 2012.

Oji Y, Inohara H, Nakazawa M, Nakano Y, Akahani S, Nakatsuka S, et al. Overexpression of the Wilms' tumor gene WT1 in head and neck squamous cell carcinoma. Cancer Sci 2003;94:523-9.

Oji Y, Suzuki T, Nakano Y, Maruno M, Nakatsuka S, Jomgeow T, et al. Overexpression of the Wilms' tumor gene WT1 in primary astrocytic tumors. Cancer Sci 2004;95:822-7.

Oka Y, Tsuboi A, Taguchi T, Osaki T, Kyo T, Nakajima H, et al. Induction of WT1 (Wilms' tumor gene)-specific cytotoxic T lymphocytes by WT1 peptide vaccine and the resultant cancer regression. Proc Natl Acad Sci (USA) 2004;101(38):13885-90.

Oka Y, Kawase I. Cancer antigen WT1-targeting treatment for the malignancies - Development of WT1 peptide vaccine. Jpn J Clin Immunol 2008;31(5):375-82.

Rezvani K, Yong AS, Mielke S, Savani B, Musse L, et al. Leukemia-associated antigen-specific T-cell responses following combined PR1 and WT1 peptide vaccination in patients with myeloid malignancies. Blood 2008;111(1):236-42.

Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 2008;26(2):190-5.

Soeda A, Morita-Hoshi Y, Kaida M, Wakeda T, Yamaki Y, Kojima Y, et al. Long-term administration of Wilms Tumor-1 peptide vaccine in combination with gemcitabine causes severe local skin inflammation at injection sites. Jpn J Clin Oncol 2010;40(12):1184–8.

Sudo T, Kamikawaji N, Kimura A, Date Y, Savoie CJ, Nakashima H, et al. Differences in MHC class I self peptide repertoires among HLA-A2 subtypes. J Immunol 1995;155:4749-56.

Sugiyama H. Cancer immunotherapy targeting Wilms' tumor gene WT1 product. Expert Rev Vaccines 2005;4(4):503-12.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009;15(23):7412-20.

Zhang HG, Pang XW, Shang XY, Xing Q, Chen WF. Functional supertype of HLA-A2 in the presentation of Flu matrix p58-66 to induce CD8+ T-cell response in a Northern Chinese population. Tissue Antigens 2003; 62:285-95.

19. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. **Requirements for Testing**

ECG equipment and supplies will be provided by ECG Vendor and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The site personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a patient's ECGs throughout the period of their participation in the study.
- Indelible ink will be used to mark the placement of the leads on the skin to ensure consistent placement throughout the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. **Patient Restrictions and Instructions**

- Prior to ECG acquisition, the patient will have rested 10 minutes in the supine position and will remain so until the ECG is obtained.

3. **Reporting**

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine patients' eligibility or continuance in the study.
- ECGs will be reviewed (signed and dated as necessary when an electronic system is not used) by an Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given patient whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the site for review and signature.
- The ECG tracing will be kept with patient's source documentation and / or CRF unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the site.

4. **Data Standardization**

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

20. APPENDIX II. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Performance Status
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, eg, 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 MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-55, 1982.

21. APPENDIX III. NEW YORK HEART ASSOCIATION [NYHA] FUNCTIONAL CLASSIFICATION

Class	Functional Capacity
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256. excerpted on American Heart Association [homepage on internet]. Dallas, TX, US [updated 18 Mar 2011; cited 14 Dec 2011]. Available from: http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

22. APPENDIX IV. CLINICAL LABORATORY TESTS

The following laboratory tests are to be performed:

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)

Hemoglobin, Hematocrit, Platelet Count, Red Blood Cell (RBC) Count, White Blood Cell (WBC) Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES:

Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

URINALYSIS:

Blood, Glucose, Ketones, Leukocyte esterase, Nitrites, pH, Protein
Microscopic examination will be conducted if blood or protein is 2+ or higher.

OTHER TESTS:

Hepatitis B Ag[a], Hepatitis C Ab[a], Serum Pregnancy (β-HcG) (in female patients of child-bearing potential only), HIV-1 Ab[a], HIV-2 Ab[a].

[a] For patients with any signs or symptoms suggestive of infection.

Laboratory reports will be initialed and dated on all pages by a 1572-listed investigator (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. Possibly study drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

LABORATORY TESTING SCHEDULE

Laboratory testing to be performed at each visit is indicated in Appendix Table 8 for Part 1 of the study and Appendix Table 9 for Part 2 of the study.

Appendix Table 8: Schedule of Clinical Laboratory Tests – Part 1

	Screening	Vaccine Induction Phase					Consolidation Phase				Maintenance Phase	End of Study
		1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose	7th dose	8th dose	9th dose		
Test		Day 1 (-1)	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 29 (-1)	Day 43 (±2)	Day 57 (±2)	Day 71 (±2)	Day 85 (±2)	every 28 (+7) days	within 28 days after last dose
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X		X	X	X	X	X	X	X
Hepatitis B Ag[a]	X											
Hepatitis C Ab[a]	X											
HIV-1[a]	X											
HIV-2[a]	X											
Serum Pregnancy (β-HcG)[b]	X	X										X

[a] For patients with any signs or symptoms suggestive of infection.
[b] For female patients of child-bearing potential only.

Appendix Table 9: Schedule of Clinical Laboratory Tests – Part 2

	SCR	Vaccine Induction Phase									Consolidation Phase						Maintenance Phase	End of Study
		1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose	7th dose	8th dose	9th dose	10th dose	11th dose	12th dose	13th dose	14th dose	15th dose		
		Day 1 (-1)	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 29 (-1)	Day 36 (-1)	Day 43 (-1)	Day 50 (-1)	Day 57 (-1)	Day 71 (±2)	Day 85 (±2)	Day 99 (±2)	Day 113 (±2)	Day 127 (±2)	Day 141 (±2)	every 28 (+7) days	within 28 days after last dose
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X		X		X		X	X	X	X	X	X	X	X	X
Hepatitis B Ag[a]	X																	
Hepatitis C Ab[a]	X																	
HIV-1[a]	X																	
HIV-2[a]	X																	
Serum Pregnancy (β-HcG)[b]	X	X																X

Abbreviations: SCR = screening

[a] For patients with any signs or symptoms suggestive of infection.

[b] For female patients of child-bearing potential only.

23. APPENDIX V. BIOMARKER SAMPLING AND PROCESSING

BIOMARKER SAMPLING SCHEDULE

Biomarker samples to be collected at each visit are indicated in Appendix Table 10 for Part 1 of the study and Appendix Table 11 for Part 2 of the study. Procedures for sample processing and handling are detailed in separate manuals.

Appendix Table 10: Schedule of Biomarker Sampling – Part 1

	Screening	Vaccine Induction Phase							Consolidation Phase					Maintenance Phase	End of Study
		1st dose		2nd dose	3rd dose	4th dose	5th dose		6th dose	7th dose	8th dose	9th dose			
Biomarker		Day 1 (-1)	Day 3	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 29 (-1)	Day 31	Day 43 (±2)	Day 57 (±2)	Day 71 (±2)	Day 85 (±2)	Day 87	every 28 (+7) days	within 28 days after last dose
DTH Skin Test Evaluation		X	X				X	X				X	X		X
Blood for CTL	X	X		X	X	X	X		X	X	X	X		X	X
Blood for Anti-WT1 Antibody		X			X		X			X		X		X[a]	X
Blood for PBMC isolation		X					X								X
Blood for retrospective biomarker analyses		X	X	X	X		X			X		X		X[a]	X
IHC Tumor Tissue Samples[b]	X														X[c]

Abbreviations: CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, IHC = immunohistochemistry, PBMC = peripheral blood mononuclear cell, WT1 = Wilms' tumor

[a] Perform every 2nd dosing day starting after the 9th dose.

[b] In place of tumor tissue samples from a biopsy during screening, archived tumor tissue samples may be provided. Availability of tumor tissue samples should be determined during screening through provision of the accession number or other identification number. If necessary, the tumor tissue sample biopsy should be performed after study eligibility has been confirmed and before the first dose of study drug. The tumor tissue samples will only be provided to the sponsor for patients who receive study drug. In place of archival tumor tissue samples, patients with AML should have available the results from a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. For patients with AML, bone marrow aspirations/biopsies are scheduled when clinically indicated, however peripheral blood assessed for blasts and WT1 transcript at least at baseline and every scheduled tumor assessment.

[c] Biopsy for tumor tissue samples after the last dose of study drug is not mandatory. Tumor samples will be obtained from all patients who provided consent. IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.

Appendix Table 11: Schedule of Biomarker Sampling – Part 2

	SCR	Vaccine Induction Phase											
		1st dose		2nd dose	3rd dose	4th dose		5th dose		6th dose	7th dose	8th dose	9th dose
Biomarker		Day 1 (-1)	Day 3	Day 8 (-1)	Day 15 (-1)	Day 22 (-1)	Day 27	Day 29 (-1)	Day 31	Day 36 (-1)	Day 43 (-1)	Day 50 (-1)	Day 57 (-1)
DTH Skin Test Evaluation		X	X				X	X	X				
Blood for CTL	X	X		X	X	X		X		X	X	X	X
Blood for Anti-WT1 Antibody		X			X			X					X
Blood for PBMC isolation		X						X					
Blood for retrospective biomarker analyses		X	X	X	X			X					X
IHC Tumor Tissue Samples[b]	X												

Appendix Table 11: Schedule of Biomarker Sampling – Part 2 (Continued)

	Consolidation Phase								Maintenance Phase	End of Study
	10th dose		11th dose		12th dose	13th dose	14th dose	15th dose		
Biomarker	**Day 71 (±2)**	**Day 83**	**Day 85 (±2)**	**Day 87**	**Day 99 (±2)**	**Day113 (±2)**	**Day 127 (±2)**	**Day141 (±2)**	**every 28 (+7) days**	**within 28 days after last dose**
DTH Skin Test Evaluation			X	X						X
Blood for CTL	X		X		X	X	X	X	X	X
Blood for Anti-WT1 Antibody			X			X		X	X[a]	X
Blood for PBMC isolation										X
Blood for retrospective biomarker analyses			X			X		X	X[a]	X
IHC Tumor Tissue Samples[b]										X[c]

Abbreviations: CTL = cytotoxic T lymphocyte induction activity, DTH = delayed-type hypersensitivity reactivity, IHC = immunohistochemistry, opt = optional, PBMC = peripheral blood mononuclear cell, SCR = screening, WT1 = Wilms' tumor

[a] Perform every 2nd dosing day during the Maintenance Phase.

[b] In place of tumor tissue samples from a biopsy during screening, archived tumor tissue samples may be provided. Availability of tumor tissue samples should be determined during screening through provision of the accession number or other identification number. If necessary, the tumor tissue sample biopsy should be performed after study eligibility has been confirmed and before the first dose of study drug. The tumor tissue samples will only be provided to the sponsor for patients who receive study drug. In place of archival tumor tissue samples, patients with AML should have available the results from a bone marrow aspirate and/or bone marrow biopsy with PCR for WT1 transcript performed before the first dose of study drug. Patients with AML should also have peripheral blood assessed for blasts and WT1 transcript.

[c] Biopsy for tumor tissue samples after the last dose of study drug is not mandatory. Tumor samples will be obtained from all patients who provided consent. IHC need not be performed for patients with AML provided RT-PCR for WT1 transcript is assessed.

24. APPENDIX VI. STUDY DRUG PREPARATION

The following is a summary of the study drug preparation procedures. Complete instructions are provided in the Pharmacy Manual.

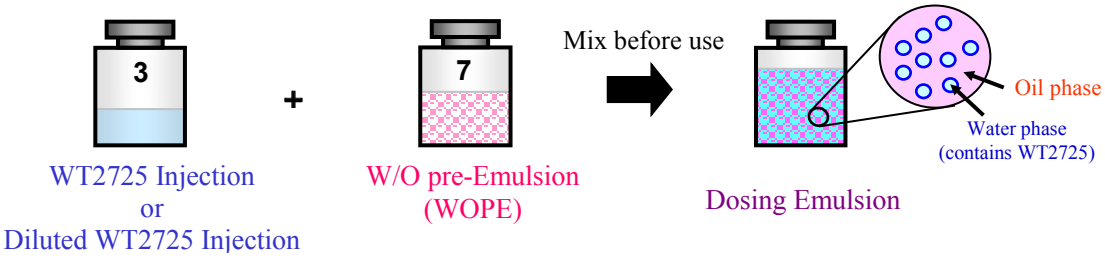
Warning: When handling WT2725 Injection, Diluting Solution for WT2725 Injection (DSWI), and W/O pre-Emulsion (WOPE) wear proper protective equipment including gloves and safety glasses or goggles. Use standard procedures for investigational medications.

The study drug contains 4 components that may be diluted prior to administration.

1. WT2725 Injection 50 mg/mL
2. WT2725 Injection 2 mg/mL
3. Diluting Solution for WT2725 Injection (DSWI)
4. W/O pre-Emulsion (WOPE)

At the clinical site, WT2725 Injection (2 mg/mL and/or 50 mg/mL) is diluted to an appropriate concentration using DSWI, if needed. Subsequently, WT2725 Injection or diluted WT2725 Injection is mixed with the WOPE at a ratio of 3:7 (by volume) to form the Dosing Emulsion (Appendix Figure 6). The Dosing Emulsion (Drug Product) is a white liquid emulsion and will be administered by sc injection.

Appendix Figure 6: Description of WT2725 Dosing Emulsion (Drug Product) Preparation



The following dose cohorts are planned for Part 1 of the study:

DTH skin test injections only: 0.01 mg WT2725 in diluted WT2725 Injection (0.05 mL x 1 site, id) and Control (Diluting Solution for WT2725 Injection [DSWI]) (0.05 mL x 1 site, id)

Cohort 1: 0.3 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)

Cohort 2: 0.9 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)

Cohort 3: 3.0 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)

Cohort 4: 9.0 mg WT2725 in Dosing Emulsion (0.3 mL x 2 sites for a total volume of 0.6 mL per patient, sc)

Patients in the RP2D cohorts will initiate treatment at the RP2D (9.0 mg).

The following dose cohorts are planned for Part 2 of the study:

Cohort 5: 18.0 mg WT2725 in Dosing Emulsion (0.6 mL x 2 sites for a total volume of 1.2 mL per patient, sc)

Cohort 6: 27.0 mg WT2725 in Dosing Emulsion (0.9 mL x 2 sites for a total volume of 1.8 mL per patient, sc)

All study drug components (WT2725 Injection 50 mg/mL, WT2725 Injection 2 mg/mL, Diluting Solution for WT2725 Injection [DSWI], and W/O pre-Emulsion [WOPE]) should be stored under refrigeration (cold temperature 2°C to 8°C), and protected from light and freezing. All drug products must be prepared and stored under ambient conditions on the day of dosing, and used or discarded within 6 hours following preparation of the drug product.

Following is a descriptive procedure to prepare diluted WT2725 Injection for DTH skin test injections (Appendix Table 12):

Preparation of 0.2 mg/mL WT2725 Injection for DTH skin tests: Add 0.1 mL of WT2725 Injection 2 mg/mL to DSWI and mix with a vortex mixer to obtain a 0.2 mg/mL WT2725 Injection for DTH skin test.

Preparation of Control Solution for DTH skin tests: Withdraw 0.05 mL from a vial of the DSWI to obtain the Control Solution for DTH skin test.

Following is a descriptive procedure to prepare varying concentrations of Dosing Emulsion (Drug Product) for clinical administration (Appendix Table 12) in Parts 1 and 2 of the study:

a. Preparation of 0.5 mg/mL Dosing Emulsion for Dose cohort 1: Add 0.2 mL of DSWI to WT2725 Injection 2 mg/mL and mix with a vortex mixer. Withdraw 0.3 mL of diluted WT2725 Injection, add to the WOPE and mix with a vortex mixer to obtain a 0.5 mg/mL Dosing Emulsion.
b. Preparation of 1.5 mg/mL Dosing Emulsion for Dose cohort 2: Add 0.1 mL of WT2725 Injection 50 mg/mL to the DSWI and mix with a vortex mixer. Withdraw 0.3 mL of diluted WT2725 Injection, add to the WOPE and mix with a vortex mixer to obtain 1.5 mg/mL Dosing Emulsion.
c. Preparation of 5 mg/mL Dosing Emulsion for Dose cohort 3: Add 0.45 mL of WT2725 Injection 50 mg/mL to the DSWI and mix with a vortex mixer. Withdraw 0.3 mL of diluted WT2725 Injection, add to the WOPE and mix with a vortex mixer to obtain 5 mg/mL Dosing Emulsion.
d. Preparation of 15 mg/mL Dosing Emulsion for Dose cohort 4, 5, and 6: Add 0.3 mL of WT2725 Injection 50 mg/mL to the WOPE and mix with a vortex mixer to obtain 15 mg/mL Dosing Emulsion

The following items will be supplied for preparation of DTH skin test injection and Dose cohorts 1 to 6:

- 1 mL syringes

- 24 G needle
- Vortex mixer

The following items will be supplied for withdrawal and administration of DTH skin test injection and Dose cohorts 1 to 6:

- 1 mL syringes
- 25 - 27 G needle
- Vortex mixer

Appendix Table 12: Preparation of WT2725 Dosing Emulsion (Drug Product) – Parts 1 and 2

Dose cohort #	Dose (mg/body)	WT2725 concentration in Dosing Emulsion (mg/mL)	Dilution of WT2725 Injection	
			Volume of WT2725 Injection added into a vial of DSWI (mL)	WT2725 concentration prior to mixing with WOPE (mg/mL)
DTH skin test[a]	0.01		0.1 mL of WT2725 Injection 2 mg/mL	NA (Not mixed with WOPE)
1	0.3[b]	0.5	0.2 mL of DSWI is added to a vial of WT2725 Injection 2 mg/mL (1.0 mL/vial)	1.667 (dilution by 1.2)
2	0.9[b]	1.5	0.1 mL of WT2725 Injection 50 mg/mL	5 (dilution by 10)
3	3.0[b]	5	0.45 mL of WT2725 Injection 50 mg/mL	16.67 (dilution by 3)
4	9.0[b]	15	No dilution of WT2725 Injection 50 mg/mL (ie, 0.3 mL of WT2725 Injection 50 mg/mL is mixed directly with WOPE)	50 (Not diluted)
5	18.0[c]	15	No dilution of WT2725 Injection 50 mg/mL (ie, 0.3 mL of WT2725 Injection 50 mg/mL is mixed directly with WOPE)	50 (Not diluted)
6	27.0[d]	15	No dilution of WT2725 Injection 50 mg/mL (ie, 0.3 mL of WT2725 Injection 50 mg/mL is mixed directly with WOPE)	50 (Not diluted)

Abbreviations: DSWI = Diluting Solution for WT2725 Injection, DTH = delayed-type hypersensitivity, NA = not applicable, sc = subcutaneous, W/O = water-in-oil, WOPE = W/O pre-Emulsion

[a] DTH skin test: 0.05 mL × 1 site (DTH testing solution is prepared by adding 0.1 mL of WT2725 Injection 2 mg/mL to a vial of DSWI).

[b] 0.3 mL × 2 sites for a total volume of 0.6 mL per patient

[c] 0.6 mL × 2 sites for a total volume of 1.2 mL per patient

[d] 0.9 mL × 2 sites for a total volume of 1.8 mL per patient

25. APPENDIX VII. DTH SKIN TEST PROCEDURES

DTH skin tests and evaluations will be performed at the times indicated on the Schedules of Assessments (Tables 3 - 6). At each time point indicated, both diluted WT2725 Injection for DTH skin test and the control will be administered and evaluated.

Administration of diluted WT2725 Injection for DTH skin test:

Use the diluted WT2725 Injection for DTH skin test (refer to Appendix VI for preparation).

Perform intradermal injection of 50 µL (10 µg) into the forearm.

Administration of control for DTH skin test:

Use the Diluting Solution for WT2725 Injection (refer to Appendix VI for preparation).

Perform intradermal injection of 50 µL into the same forearm at a site that is a distance of at least 10 cm or more away from the dosing site of the diluted WT2725 Injection for DTH skin test.

In the event of an immediate hypersensitivity reaction, future dosing should be evaluated by the investigator and medical monitor.

Approximately 48 hours (but no sooner than 24 hours) following the skin test injections, evaluate DTH reactions:

For each site of the DTH skin test injection visually inspect the test site and palpate the area:

- measure the area of erythema, if any, at the 2 injection sites, across the long and short diameters
- evaluate the quality of the reaction, such as redness, induration, ulceration, etc, if any, at the 2 injection sites

If the DTH reactivity results in erythema with induration greater than 2 cm or leads to ulceration of the skin test site, further DTH testing should not be conducted for the patient.

26. APPENDIX VIII. DEFINITIONS FOR REPORTING ADVERSE EVENTS

The Investigator must assess the severity of the AE using the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 (NCI 2009).

The Investigator must assess the relationship of the AE to the study medication using the following:

- **Not related** – improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Possible** - occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
- **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
- **Definite** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The action taken regarding study drug will be defined as follows:

- **Dose Not Changed** – no change.
- **Dose Reduced.**
- **Dose Increased.**
- **Drug Interrupted** – study drug stopped temporarily.
- **Drug Withdrawn** – study drug stopped permanently.
- **Not Applicable.**