Protocol *(*D8350004*)*

Initial Phase I Study of WT2725 Dosing Emulsion in Patients with Advanced Malignancies

Statistical Analysis Plan
Version 2.0
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This template for Sunovion Pharmaceuticals, Inc. Statistical Analysis Plans (SAPs) follows the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) E3 guidelines on the Structure and Content of Clinical Reports (July 1996)

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	*Description*
β - HcG	β-human chorionic gonadotropin
AEs	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transferase
AML	Acute myeloid leukemia
AST	Aspartate transferase
BMI	Body mass index
BUN	Blood urea nitrogen
CA-125	Cancer antigen 125
CI	Confidence interval
CR	Complete remission
CRc	Composite complete remission
CRi	Complete remission with persistence of cytopenias
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTL	Cytotoxic T lymphocyte
CTMS	Clinical trials management system
DLT	Dosing-limiting toxicity
DOR	Duration of response/remission
DTH	Delayed-type hypersensitivity reaction
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHC	Immunohistochemistry
IPD	Important Protocol Deviations
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRC	Immune-related response criteria
irSD	Immune-related stable disease
IWG	Modified International Working Group
KM	Kaplan Meier

MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response/remission
PT	Preferred term
QT_{c-B}	Corrected QT interval, using Bazett's (square root) correction
QT_{c-F}	Corrected QT interval, using Fridericia's (cube root) correction
RBC	Red blood cell
RP2D	Recommended phase 2 dose
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD (2)	Standard deviation; Stable disease
SE	Standard error
SOC	System Organ Class
SI	International System of Units
SPD	Sum of the product of the 2 largest perpendicular diameters
TEAE	Treatment-emergent adverse event
TTP	Time to progression
US	United States
WBC	White blood cell
WHO	World Health Organization
WT1	Wilms' tumor gene 1

2. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Sunovion Pharmaceuticals Inc. Protocol D8350004, "Initial Phase 1 Study of WT2725 Dosing Emulsion in Patients with Advanced Malignancies".

This is a Phase 1, open-label, dose-escalation study in adult patients with advanced malignancies known to overexpress the Wilms' tumor gene 1 (WT1) protein. The study will primarily evaluate dosing-limiting toxicity (DLT) and define the maximum tolerated dose (MTD) of WT2725 Dosing Emulsion during the DLT Evaluation Period. Patients may remain on study drug until confirmed progressive disease, intolerance to treatment with study drug, or fulfillment of any of the other criteria for discontinuation. The primary endpoints will be based on the occurrence of DLT and adverse events (AEs), and the findings from clinical laboratory tests, vital signs measurements, body weight measurements, and electrocardiogram (ECG) results.

This SAP should be read in conjunction with the study protocol version 7 (December 3rd, 2014) and case report form (CRF) dated January 26th, 2015..

3. STUDY OBJECTIVES

3.1. 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.

3.2. Secondary Objectives

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 (IWG) response criteria in acute myeloid leukemia [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.

3.3. 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.

4. STUDY DESIGN

4.1. General Description

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 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 (see Figures 1 and 2):

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)

Figure 1: Study Schematic – Part 1

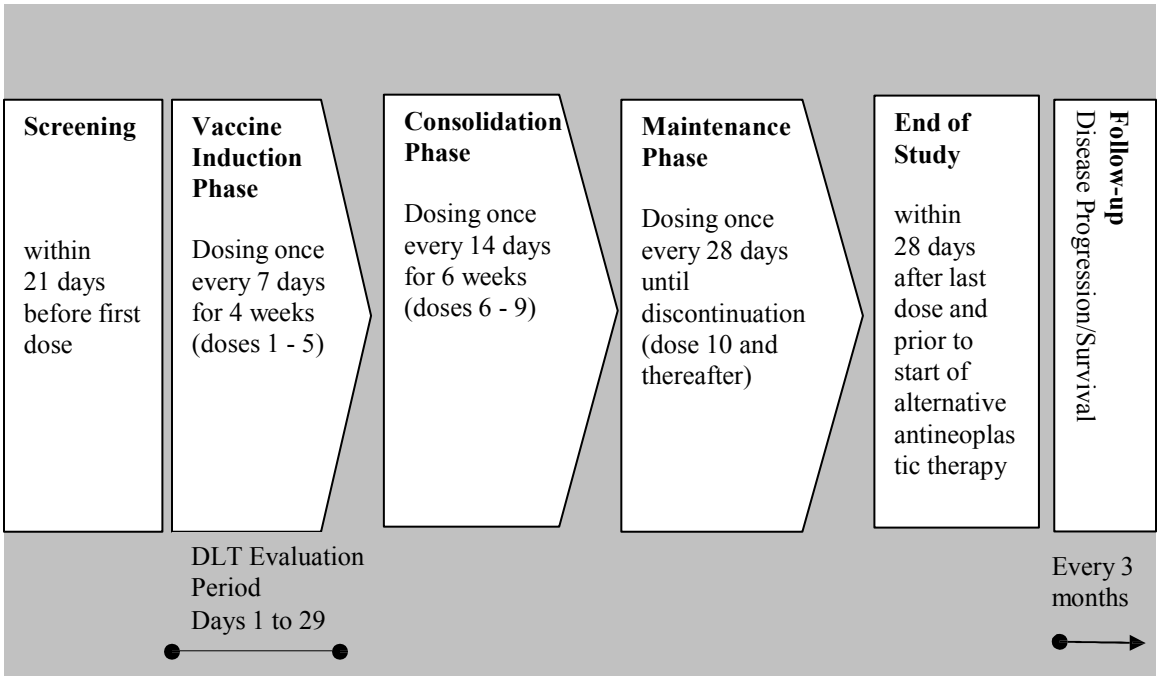
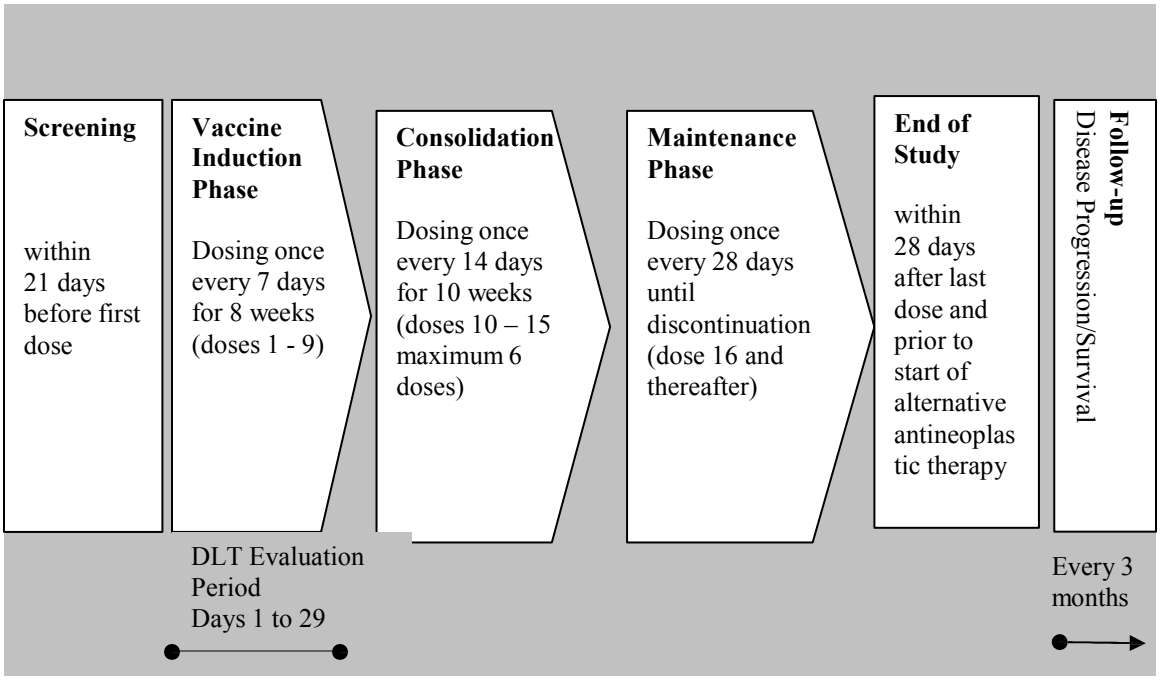


Figure 2: Study Schematic – Part 2



The following dose cohorts are planned for this study.
Part 1:

- 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:

- 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.

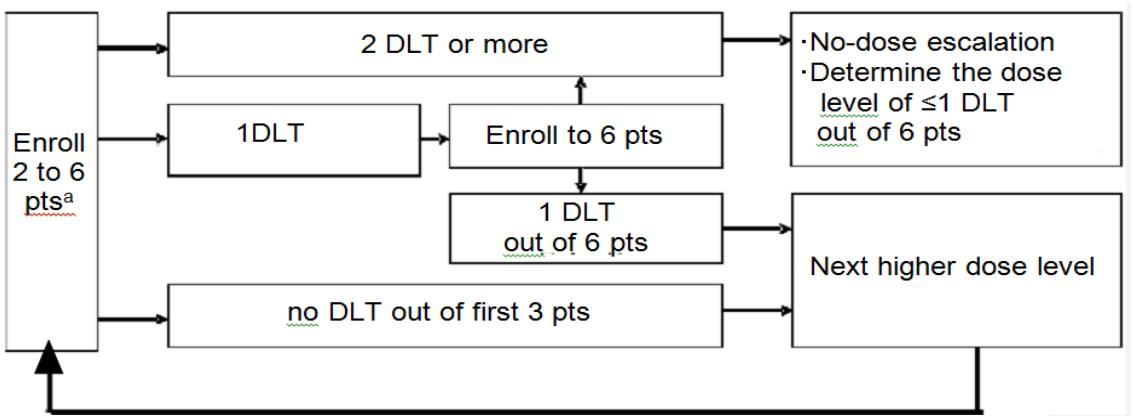
Approximately 60 to 80 patients total in Parts 1 and 2 including replacements will be dosed in this clinical trial. Part 1: 4-8 clinical sites in the United States (US) and Part 2: an additional 2 sites in US may be utilized to enroll patients.

The following list contains the definitions of some important terminology in this study:

- DLT: defined as any Grade 3 or greater AE that occurs after the administration of study drug during the DLT Evaluation Period that is 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). AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 (National Cancer Institute [NCI]-2009).
- 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.
- An evaluable patient: defined as a patient who has a DLT or a patient who completes the DLT Evaluation Period without the occurrence of a DLT.
- MTD: defined as the dose at which no more than 1 of 6 patients experiences a DLT when 2 or more of 2 to 6 patients experiences a DLT at the next higher dose cohort.

4.1.1. Dose Cohort Escalation

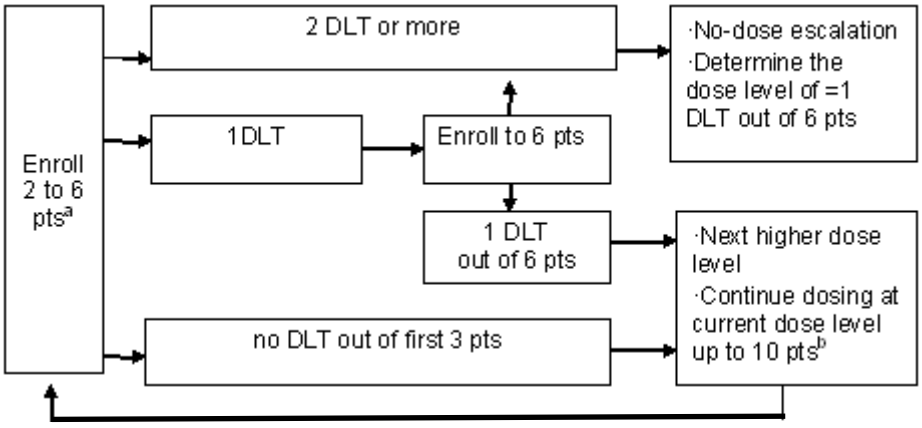
Figure 3: Dose Escalation Scheme – Part 1



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.

Figures 3 and 4 illustrate the planned dose cohort escalation scheme.

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 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 subjects 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.

4.1.2. Dose Cohort 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 the MTD has been determined or approximately 10 patients have been enrolled at both planned dose levels.

4.1.3. Dose Adjustment Criteria

The following section provides guideline for intra-patients dose adjustment.

4.1.3.1. Dose Reduction Criteria

- No dose reduction is permitted for the lowest dose cohort, 0.3 mg, at any time.

- Patients who experience DLT may remain on the study at a reduced dose (reduced to the next lower dose level), which will be addressed on a case by case basis. Patients who require a second reduction in 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 (after the DLT evaluation period) 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.

4.1.3.2. 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.

4.2. Blinding

This is an open-label study. No randomization or blinding procedure will be performed. Sequential cohorts of patients will be treated according to the dose escalation scheme and stopping criterion described in Section 4.1.1 and 4.1.2.

4.3. Determination of Sample Size

The total sample size for the study will be determined by the number of patients treated in each dose cohort and the number of dose cohorts necessary to determine the MTD.

5. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Not applicable.

6. EFFICACY AND SAFETY VARIABLES

6.1. Schedule of Assessments

Table 1: 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 1: 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 of protocol).

[b] All patients should complete an End of Study visit (see Table 2) 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 Appendix IV of protocol 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 2: 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	

Table 2: 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 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	
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 of protocol).

[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 Appendix IV of protocol 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.

[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 3: Schedule of Assessments for Screening and Vaccine Induction Phase – Part 2

	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)**
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]											

Table 3: 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)**
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]
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]

Table 3: 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)
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

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

[b] All patients should complete an End of Study visit (see 4) 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 Appendix IV of protocol 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.

Footnotes continued on the next page.

[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 subjects who receive study drug. In place of archival tumor tissue samples, subjects 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 4: 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	

Table 4: 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
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[c]	X[c]		X	
Blood sample for Anti-WT1 antibody			X[c]			X[c,k]		X[c,k]	X[c,k]		X	
Blood sample for retrospective biomarker analyses			X[c]			X[c,k]		X[c,k]	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]	

Table 4: 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
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

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

The window algorithm rules will be only applied to the unscheduled assessments. For scheduled assessments (except CA-125 that is mapped according to the schedule of tumor assessment), they will be kept as what they are recorded according to the schedule of assessments in protocol. The window algorithm is described as follows. For an unscheduled assessment, based on its relative study day with respect to the date of the first dose, map it to the nearest scheduled assessment according to Day described in the schedule of assessments in protocol. If there is already a scheduled assessment, keep this unscheduled assessment as unscheduled assessment.

6.2. Primary Endpoint Variables

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 ECG results.

The determination of the MTD of WT2725 Dosing Emulsion will be based on the incidence of DLT at each dose escalation cohort and the overall safety profile of WT2725 Dosing Emulsion. The incidence of DLT will be evaluated during the DLT Evaluation Period.

6.3. Secondary Endpoint Variables

- Proportion of patients in each overall response category for each dose cohort based on irRC, modified IWG, and/or tumor markers, as appropriate, for all posttreatment tumor assessments.
- Percent change in tumor burden from baseline to each posttreatment 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.
    - DTH to the WT2725 peptide at each assessment time.
    - Measurement of level of expression of CD8+, Foxp3, human leukocyte antigen (HLA) class I, and WT1 protein in tumor tissue using immunohistochemistry (IHC) methods

6.4. Exploratory Variables

- 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.

6.5. Additional Exploratory Endpoints

Progression-free survival (PFS), time to progression (TTP) and duration of response will be summarized for solid tumor patients. Duration of Composite Complete Remission (CRc), duration of response (CRc + partial remission [PR]), and time to progression for AML (TTP_{AML}) will be summarized for AML patients. Overall survival (OS) will be summarized for all patients and by disease category (solid tumor vs. AML).

6.6. Safety Assessments

Safety assessments will be conducted at each study visit as indicated on the Schedules of Assessments (Table 1 and Table 2) 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.

6.7. Drug Concentration Measurements

Not Applicable.

7. STATISTICAL METHODS

7.1. General Methodology

Continuous variables will be summarized by mean, standard deviation, 25th percentile, median (50th percentile), 75th percentile, minimum and maximum values. Categorical variables will be summarized using counts and percentage. In general, data will be summarized by enrolled or starting dose cohort. Efficacy data will also be summarized by tumor type and/or outcome measurement.

All raw data will be presented to the original number of decimal places. The means, medians, and percentiles will be presented to 1 more decimal place than the raw data. The standard deviations will be presented to 2 more decimal places than the raw data.

Due to the small sample size of the study, the Wilson Score 95% confidence intervals (CIs) will be used in the summary for the binomial proportion of the derived best overall response for both solid tumor irRC patients and the AML patients, separately. This interval is obtained using the following formula and further details are presented in

reference [Newcombe-1998]: $(2np + z^2 +/- z\sqrt{[(z^2 + 4npq)]}/2(n + z^2)$, where n=total sample size, p=observed probability of "success", q=1-p and z= 1- α/2 point of the standard Normal distribution.

The Spearman's rank correlation will be calculated for specified exploratory endpoints (or biomarkers). This will be carried out using the CORR procedure in SAS v9.1.3 or higher.

7.2. Adjustments for Covariates

Not applicable.

7.3. Handling of Dropouts or Missing Data

Missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted.

Adverse event and concomitant medication dates will be imputed as follows:

Start Date: If only 'day' is missing, and the month and year are not the same as the month and year of first dose, then impute day with '01'. Otherwise, if the month and year are the same as first dose date, use first dose date. If 'day' and 'month' are missing, and 'year' is not missing, then impute month and day with month and day of first dose date (assuming same 'year'). If the year is not the same as the year of first dose, impute 01 for day and 01 for month. If the start date is completely missing, it will be set to the first dose date.

Stop Date: If only 'day' is missing, impute day with last day of the month. If 'day' and 'month' are missing, and 'year' is not missing, then impute month with '12' and day with '31' (or date of study discontinuation/completion if earlier than 12-31). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs.

Note, for all listings the actual value for date (not imputed) will be presented in all data listings and imputed dates will only be used for programming flags, etc.

7.4. Interim Analyses and Data Monitoring

Not applicable.

7.5. Multicenter Studies

There will be 4 to 8 investigative sites involved. The number and percentage of patients will be presented for each center. However, no other statistics will be presented by center and the data will be pooled together for the analysis.

8. STATISTICAL ANALYSIS

In this section and all after, when tables are presented by posttreatment visits, the last visit will be the visit at the end of study. When applicable, visits after the start of the maintenance phase and unscheduled visits will be included in a summary of maximum and minimum values observed for each patient's posttreatment visits, i.e., the minimum and maximum values are based on all the post treatment visits.

In general descriptive statistics for continuous variables will be summarized by the mean, standard deviation, 25^{th} percentile, median (50^{th} percentile), 75^{th} percentile, minimum and maximum values. When continuous variables are displayed for less than 3 patients, only the number of observations will be presented. Categorical variables will be summarized using counts and percentages.

All raw data will be presented to the original number of decimal places. The means and medians will be presented to 1 more decimal place than the raw data. The standard deviations will be presented to 2 more decimal places than the raw data.

Baseline will generally be defined as data obtained as the last non-missing value prior to the first dose of study drug, i.e., including the pre-dose assessment on Day 1, assessments during screening and other assessments prior to the first dose of study drug.

AE tables and laboratory tables will be presented by visits and by tumor group. Tumor groups are defined as groups of overall, solid tumor, and AML patients.

Unless otherwise stated, summaries will be produced by dose cohort, which is defined as the intended and starting dose to which the patient was enrolled.

8.1. Disposition of Patients

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.

A tabulation of the number and percentage of patients treated at each center will be presented. Additionally, a summary of the number of patients starting each dose within each treatment phase will be presented.

A listing of all patients discontinued from the study will be presented by dose cohort including a patient identifier, treatment center, the specific reason for discontinuation, and the duration of treatment before discontinuation.

8.2. Important Protocol Deviations

Important Protocol Deviations (IPD) will be identified and documented based on a review of potentially IPDs. Potential Important Protocol
Deviations will be defined as those collected with a significance of "major". The potential IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. Potential IPDs will be assessed as to whether or not they have a significant impact on the assessment of safety or efficacy. The IPD categories include, but are not limited to:

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

Per PRA processes, IPD data will be entered into PRA's Clinical Trials Management System (CTMS). The study team and the sponsor will conduct ongoing reviews of the IPD data from CTMS and the resulting set of evaluable patients throughout the study, adjusting the IPD criteria as appropriate. The evaluable patients set should be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

Specific IPDs, category codes and deviation codes are outlined in the Protocol Deviation Guidance document as noted in the Clinical Management Plan.

The number of patients with each type of IPD will be tabulated by deviation category and by deviation type for all patients in the Safety population by dose cohort. A listing of all deviations including deviation date, deviation type, significance (major vs minor), deviation description and any relevant comments will be generated.

8.3. Analysis Populations

There are 3 planned analysis populations.

- Safety population: includes 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
- DLT population: includes all patients in the Safety population who experience a DLT within the DLT evaluation period or completed the DLT evaluation without experiencing a DLT and will be used for analysis of DLT.
- Efficacy population : include all patients in the Safety population who are evaluable for response (for each irRC, IWG, CA-125 and WT1 by RT-PCR)
    - Population for irRC response: including all the patients in the Safety population who are not AML patients and whose lesions are measureable and have at least one posttreatment assessment. (Note that any posttreatment irRC assessment is based on the baseline assessment)
    - Population for modified IWG response: includes all the AML patients in the Safety population who have >5% marrow blasts or >50 copy/μg RNA of quantitative RT-PCR for WT1 transcript before the first date/time of study drug and who have at least one posttreatment assessment.
    - Population for CA-125 tumor marker: including all ovarian cancer patients in the Safety population who have a baseline CA-125 assessment and at least one assessment posttreatment.
    - Population for WT1 by RT-PCR tumor marker: includes AML patients in the Safety population who have a baseline assessment and at least one assessment posttreatment.
- Population for CTL: including all patients in the Safety population who has a baseline assessment of percentages of WT1-positive cells among CD8-positive cells and at least one post-baseline assessment

Additional populations for analyses of other tumor markers identified may be defined in a similar manner.

8.4. Demographic and Other Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the Safety analysis population by dose cohort and overall.

The number and percentage of patients will be provided for sex (male, female), ethnicity (Hispanic or Latino, Not Hispanic or Latino), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), and each Eastern Cooperative Oncology Group (ECOG) performance status.

Descriptive statistics will be provided for age and body mass index (BMI), weight and height, where BMI is calculated as follows:

$$BMI = weight(kg) / (height(m)^2).$$

General medical history information will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0. The count and percentage of patients with each medical history event will be summarized by MedDRA SOC and preferred term for all patients only (not by dose cohort). SOCs will be presented alphabetically with PTs in descending order of frequency.

Cancer history data will be summarized as number and percentage for each type of cancer. The assessment of general medical history information will be obtained during the screening period, within 21 days before the 1st dose.

Prior medication, and prior anti-cancer regimens, along with prior response information will be listed.

Prior anti-cancer regimens and prior antineoplastic therapies (radiation and surgery) along with corresponding response data will be listed for all patients.

Prior anti-cancer regimens, and prior antineoplastic therapy of both radiotherapy and surgery will be defined as having the starting date and/or the end date (if present) of the medication before the 1st dose.

8.5. Extent of Exposure

There are 3 phases of the study, Vaccine Induction Phase, Consolidation Phase, and Maintenance Phase. For Vaccine Induction Phase, a patient will be given one dosage every 7 days, 5 times. For Consolidation Phase, a patient will be given one dosage every 14 days, 4 times. For Maintenance Phase, a patient will be given one dosage every 28 days until discontinuation. All patients with at least one dose will be included in the summary. The following summary statistics related to drug exposure will be calculated by treatment phase and dose cohort, overall by cohort, and overall:

- Number and percentage of patients with dose reduction, dose escalation, and no dose modification will be presented.
- Duration of exposure, by patient, defined in weeks, is calculated as Duration (weeks) = (last dose date – first dose date + 1) / 7.
- Cumulative dose = sum of all doses administered.

A by-patient listing of study drug dosing based on the Safety population will be provided.

8.6. Analysis of Efficacy

8.6.1. Primary Analysis

To establish the safety and tolerability of WT2725 and to determine the MTD of WT2725 are the primary analyses of this study. For details see Section 8.7.1.

8.6.2. Secondary Analyses

The number and percentage of patients will be presented according to categories of irRC, IWG, and /or tumor markers of CA-125 and WT1 by RT-PCR by dose cohort displaying their best response on-study.

The baseline assessment for patients with solid tumors or AML is defined as the assessment at screening, obtained within the 28 days prior to the planned first dose of the study drug. If multiple assessments are available, the most recent one should be used.

Tumor assessments will be conducted during screening, and then every 8 weeks after the first dose of study drug. All tumor assessments may be performed within ±7 days of the scheduled assessment but must be completed before study drug is administered. 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.

A listing of patients with nonenhancing lesion assessments will be provided.

8.6.2.1. Immune-related Response Criteria (irRC)

Tumor response is based on total measurable of tumor burden in patients with solid tumors (non-AML patients). For the irRC, index and measurable new lesions are taken into account. A measurable lesion is defined as 5x5 mm or more on helical Computed Tomography (CT) scan.

At the pretreatment tumor assessment, the sum of the products of the 2 largest perpendicular diameters (SPD) of all index lesions (up to 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 (≥ 5x5 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:

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 (i.e. the SPD of all index lesions at screening).

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

- irCR (immune-related complete response) = complete disappearance of all lesion (whether measurable or not, and no new lesions) confirmed by a repeat consecutive assessment 4 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 4 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) confirmed by a repeat, consecutive assessment at least 4 weeks after the date of first documentation
- Unconfirmed irPD = Any irPD record after study day 1 and no record of irPD confirmed 4 weeks after, which include the situation that the PI can discontinue a patient from the study for the reason of PD without confirmation of PD after 4 weeks if patients have rapid symptomatic progression accompanied by a decline in performance status.

The assessment made by the investigator will be used for all summaries.

Best response is defined to be the best irRC response (irCR > irPR > irSD > irPD) evaluated after dosing until treatment discontinuation. Patients without post-baseline evaluations will be considered as unevaluable. Additional categories are defined for response (irCR + irPR) and disease control (irCR + irPR + irSD).

Tables will summarize the number and percentage of the best overall tumor response for each category by dose cohort, the number, percentage, and Wilson Score 95% CI will also be presented for the response categories of irCR, response, and disease control.

The percent change in tumor burden from baseline will be presented at each posttreatment tumor assessment graphically and in patient data listings. Percent change will be calculated as 100*[(current tumor burden - baseline tumor burden)/baseline tumor burden]. The best change, i.e., the minimum of percent change from baseline for each patient will be displayed in a waterfall plot.

A by-patient listing of irRC assessment will be provided.

8.6.2.2. 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:

- CR: Complete remission
  - 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)
- PR: 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).
- PD: Progressive disease. An increase of at least 50% in the percentage of blasts in the bone marrow aspirate with an increase of at least 10% of blasts in the bone marrow.

- No Response: None of the above criteria is met. This typically would represent patients that are refractory to treatment prior to achieving response or prior to treatment discontinuation.

Measurable disease will be defined as >5% marrow blasts. The assessment made by the investigator will be used for all summaries.

Best remission is defined to be the best measured remission status by disease assessment (Molecular CR > Cytogenetic CR > Morphologic CR > CRi > > PR > PRi > PD > No Response > Missing). Other categories are defined for CRc (CR + CRi) and disease control (CR + CRi + PR + PRi). The number and percentage for best response will be presented and the number, percentage, and Wilson Score 95% CI will also be presented for the categories of CR, CRc, and disease control. A shift table will be presented between baseline response and best response on-treatment. The order of the best response on-treatment will be Molecular CR > Cytogenetic CR > Morphologic CR > CRi > PR > PRi > PD > No Response > Missing. And the response of baseline will be classified as Molecular CR, Cytogenetic CR, Morphologic CR, CRi, Stable disease (SD). Patients who are not classified in any of Molecular CR, Cytogenetic CR, Morphologic CR or CRi will be classified as stable disease (SD). If a patient could be classified in multiple categories at baseline, the response will be chosen in the following order: Molecular CR > Cytogenetic CR > Morphologic CR > CRi > SD. All summaries will be presented overall and by dose cohort.

A by-patient listing of IWG assessment will be provided.

8.6.2.3. Tumor Markers

CA-125 and WT1 by RT-PCR will be summarized for only ovarian cancer and AML patients, respectively. Additional tumor markers may be identified and summarized as appropriate.

To evaluate the response according to CA-125, the definition of response described in Rustin, et al. [Rustin-2011] will be used. A response according to CA-125 has occurred if there is at least a 50% reduction in CA-125 levels from baseline sample. This response must be confirmed at least 28 days later by a repeat assessment that is a at least a 50% reduction or is within 10% (± 10%) using the same assay method. Additionally, the baseline must be at least 2 times the upper limit of normal and drawn within 4 weeks prior to first dose date. Progression is defined as an increase of 2 times the nadir value at any time. If the nadir is less than the upper limit of normal then a progression will be declared at 2 times the upper limit of normal. This must be confirmed at least one week

later. Not-response/Non-PD will be assessed if neither the criteria of response or progression are achieved. A table will present the number and percentage of patients for their best response (response>Not-response/Non-PD>progression) for the CA-125 population. Additionally, the percent change from baseline may be presented over time graphically.

The descriptive statistics for the log transformed RT-PCR value will be presented for bone marrow and blood separately by each assessment and by different cohort. For any assessment, if there are multiple assessments within each category (either bone marrow or blood), choose the highest one. If the result of RT-PCR is undetectable, impute it as half of 5.0 x 10 copy/ μg RNA. The percent change from baseline will be presented over time graphically for WT1 by RT-PCR for the log transformed RT-PCT values.

Additionally, other markers identified upon review may be summarized and/or categorized according to standard criteria.

A by-patient listing for both CA-125, WT1 by RT-PCR, and other tumor markers identified will be provided separately.

8.6.3. Exploratory Analyses

The Population for Biomarkers includes all patients in the Safety population who have the Day 29 biomarker assessment completed. All other exploratory analyses will use all patients in the Safety population of patients with the endpoint of interest measured at baseline and at least once posttreatment.

Biomarker sample collection will be conducted as indicated on the Schedules of Assessment (Table 1 and 2). Tables may summarize the statistics at the screening assessment, at each posttreatment visit, and at the end of study.

A table will summarize the Spearman rank correlation and 95% CI between the level of expression of WT1 protein and the degree of the immune response by dose cohort at each visit as measured by CTL induction. Additionally, the correlation at each visit may be presented graphically.

Scatter plots of maximum (mean, median) post-baseline values of immune response measured by CTL induction versus maximum (mean, median) post-baseline values of CA-125 will be presented. Additionally, scatter plots of maximum (mean, median) post-baseline values of immune response measured by CTL induction versus maximum (mean, median post-baseline values of WT1 by RT-PCR will be presented.

A listings of level of expression of WT1 protein will be provided.

If additional reports are provided by the biomarker vendor(s) then additional analyses may be performed and the vendor's report will be an appendix to the clinical study report.

8.6.3.1. CTL Evaluation

A patient is considered a CTL responder if s/he has:

- Two or more post-baseline visits (no need to be consecutive) with >=2-fold increase from baseline, if the baseline is not 0,

Or

- Only one post-baseline visit with >=2-fold increase from baseline when the total number of post-baseline visits is <=4, if the baseline value is not 0,

Or

- At least one post-baseline value > 0, if a patient has baseline of 0

A table will present the number and percentage of patients for their CTL response. Additionally, geometric mean, geometric SD, the mean, standard error (se), SD, median, 25 and 75 percentile of baseline assessments and the corresponding same descriptive statistics for both mean of post-baseline assessments for each patient and maximum of post-baseline assessments for each patient will be presented by dose cohort and overall, where geometric mean is

$$\mu_g = \sqrt[n]{A_1 A_2 \cdots A_n}.$$

and geometric SD is

$$\sigma_g = \exp\sqrt{\frac{\sum_{i=1}^{n}(\ln \frac{A_i}{\mu_g})^2}{n}}.$$

The Wilcoxon singed-rank test will be performed to see the difference between the baseline assessments and the mean of post-baseline assessments for each cohort and overall as well as the difference between the baseline assessments and the maximum of post-baseline assessments for each cohort and overall. Bar plot of mean and SE of baseline and mean of post-baseline assessments will be presented as well as baseline vs. maximum of post-baseline assessments stratified by both dose cohorts and cancer types. Similar bar plots are generated for the median and quartiles.

The percent change from baseline will be presented over time graphically. A by-patient listing will be provided.

8.6.3.2. Immune Response

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 PBMCs. 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. These results may be presented in figures and/or patient data listings.

For DTH assessments, the number of patients who have an injection with WT2725 and control will be displayed before and after injection for each dose. The number and percentage for the reaction of positive and negative based on the number of patients who have injections may also be presented for the WT2725 versus negative control. The summary for all the dose will also be generated. The patients who have at least one injection will be present. The number of positive reaction for overall is counted for the patients who have at least one positive reaction during all the doses. The number of negative reaction for overall is counted for those patients who have all negative reaction during all the doses. The corresponding percentage will also be displayed similary for each dose. The results may also be presented in data listings.
For WT1 by RT-PCR tumor marker, the descriptive statistics have been provided for the baseline, at each post-baseline assessment and change from baseline by dose cohort, including the minimum and maximum of all the post-baseline assessments.

Immunohistochemistry in tumor tissue may be evaluated by expression of CD8+, Foxp3, HLA class I, and other measurements using tumor tissue samples obtained before the first dose. Due to the sparsity of the post-baseline data, post-baseline results will only be listed but not summarized. Continuous results will be summarized in a table with mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables will be summarized in a table with frequencies and percentages. Additionally, histograms of continuous results and bar plots of categorical results will be presented.

8.6.4. Additional Exploratory Endpoints

For solid tumor patients the following endpoints will be calculated as follows:

- Progression-free survival (PFS) is defined as the time in weeks from first dose date to the date of progression or the date of death due to any cause. Patients who are alive and have not progressed by the date of analysis data cut-off will be censored at the last free evaluable tumor assessment date based on investigator

assessment. Patients with missing protocol scheduled tumor assessment(s) prior to radiologic disease progression will be considered as having disease progression on the date of the actual assessment of disease progression.

- Time to progression (TTP) is defined as the time in weeks from first dose date to the date of observed disease progression. Patients who do not have disease progression by the date of analysis data cutoff will be censored at the date of last evaluable tumor assessment based on investigator assessment.

- Duration of response (DOR) is defined as the time in weeks from the first date of response to date of first progression of disease or death in the subset of patients with an objective response of irCR or irPR. Patients who respond and have not progressed (as evaluated by investigator assessment) while on study or die will be censored at the date of their last evaluable tumor assessment. Duration of response is calculated only for patients with an objective response.

For AML patients, the following endpoints will be calculated as follows:

- Relapse is defined as
    - an investigator assessment following CRc becoming PR, PRi, PD, or No Response. The date of the worsening disease assessment will be the relapse date; or
    - an investigator assessment following PR or PRi becoming PD or No Response. The date of the worsening disease assessment will be the relapse date

- Duration of CRc: Time, in weeks, from first CRc until documented relapse and is only defined for patients who achieve CRc. Patients who die without report of relapse are considered non-events and censored at their last relapse-free disease assessment date. Patients who come off study for an allogeneic HSCT will be considered non-events and censored at the time of treatment discontinuation. Other patients who do not relapse on study are considered non-events and censored at the last relapse-free assessment date.

- Duration of disease control: Time, in weeks, from first of either PR, PRi or CRc until documented relapse of any type and is only defined for patients who achieve CRc, PR or PRi. Patients who die without report of relapse are considered non-events and censored at their last relapse-free disease assessment date. Patients who come off study for an allogeneic HSCT will be considered non-events and censored at the time of treatment discontinuation. Other patients who do not

relapse on study are considered non-events and censored at the last relapse-free assessment date.

- Time to progression for AML (TTP_{AML}) is defined as the time in weeks from first dose date to the date of observed disease progression (see Section 8.6.2.2). Patients who do not have disease progression by the date of analysis data cutoff will be censored at the date of last evaluable disease assessment based on investigator assessment.

For all patients, and by disease group, the following endpoints will be calculated as follows:

- Date of last contact will be defined as the latest of the treatment discontinuation date, last dosing administration date, last disease assessment date, end of study or the death date.

- Overall survival (OS): Time, in months, from first dose date until the date of death. Patients who do not die are censored at their date of last contact. Survival status is captured after the end of the treatment period and is also considered in determining overall survival.

- The specified time-to-event endpoints will be summarized graphically with Kaplan-Meier (KM) estimates of the survivor function and the number of patients at risk for selected timepoints. Additionally, the figures will include the median of the survival distribution and the 95% CI generated using the method of Brookmeyer and Crowley (Brookmeyer-1982). Time-to-event endpoint data will be listed grouped by tumor group. Each of the KM figures will be repeated for the Safety population as additional exploratory analyses.

For all the KM plots, the SAS output will be saved in Statistics Appendix in TFL.

8.7. Analysis of Safety

8.7.1. Dose-Limiting Toxicity (DLT)

The primary endpoint is based on the incidence of DLT at each dose cohort 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.

DLTs 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.) AEs will be graded according to the CTCAE.

The number and percentage of patients will be presented for DLT and non-DLT by each dose cohort during the DLT evaluation period. Specific DLTs are flagged in the collection of AE data and will be listed.

The number and percentage of DLT events will be presented by dose cohort and for all patients. The DLTs observed for the DLT evaluation period will be summarized by dose cohort and for all subjects by MedDRA SOC and PT. DLTs will also be summarized by category of NCI CTCAE grade.

8.7.2. Adverse Events

All AE tables summarized by MedDRA coding will be sorted alphabetically by SOC and decreasing incidence of preferred term within based on the total number of patients. AE summaries will be produced by dose cohort and tumor group.

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.

All the following summaries of AEs, unless otherwise stated, will include only TEAEs. An overall summary of AEs, including the number and percentage of patients reporting at least 1 AE, treatment-related AEs, AEs with an outcome of death (defined as CTCAE Grade 5 or outcome is "fatal"), serious AE (SAE)s, treatment-related SAEs, and AEs leading to treatment discontinuation (defined as an event with an outcome code of "drug withdrawn").

Tables will present the number and percentage of AEs by starting dose cohort and overall and by MedDRA SOC and PT for the Safety population. The following tables will be produced:

- TEAEs (including number of events and patient incidence)
- Treatment-Related TEAEs. “Related” is defined as all responses other than “Unrelated” from the CRF. 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. If in CRF, no choice is ticked, it will be treated as “Related”.
- SAEs
- Treatment-Related SAEs
- TEAEs by maximum CTCAE Grade
- TEAEs leading to treatment discontinuation
- TEAEs with outcome of death

Similar tables will also be presented by the last dose received before the start of the event. For this summary, column headers will need to include all patients who were ever dosed at that dose level. Additionally, patients may be counted more than once for each event as the events will be tabled by the last dose level received on or prior to the start date of the event.

Listings of all TEAE, AE with outcome of death, SAEs, and AEs leading to discontinuation will be presented. A separate listing for non-treatment-emergent AEs will also be provided.

8.7.3. Clinical Laboratory Evaluation

Laboratory data values will be converted to International System of (SI) units by conversion programming (detail can be found in the database conversion specifications) and delivered to the analysis and reporting group in SI units. A list of the SI units used to present laboratory data is provided in Appendix 1.

Laboratory parameters, ECOG, vital signs and ECG will be presented by tumor group for each dose cohort and within each tumor group at baseline, at each posttreatment time point before maintenance phase, and at the end of study. Data starting at the maintenance phase will be included in the summary of maximum and minimum for all visits, which will present the largest and smallest values observed for each patient posttreatment visits and the visit at the end of study.

8.7.3.1. Hematology

The following hematology tests will be summarized: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, and white blood cell (WBC) total count, WBC differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

Descriptive statistics will be provided for each test result and for change from the baseline by visit. Multiple measurements taken during the visit for a patient will be presented by the most severe value for each hematology test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered severe) if the value is within the normal limits. If the value is outside the normal limits, the value furthest from the upper or lower limit will be selected (dependent on which direction is considered severe). In the event that this algorithm does not allow for determining the most severe (i.e., a tie, etc.) the first chronological value will be selected. Low values are considered the most severe for all hematology analytes.

A by-patient listing will be provided and will flag values outside of the reference range for each lab variable.

8.7.3.2. Chemistry

The following chemistry tests will be summarized: alanine transferase (ALT), alkaline phosphatase (ALP), aspartate transferase (AST), bicarbonate, bilirubin (total, direct, indirect), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, protein (total), sodium, uric acid, and albumin.

Descriptive statistics will be provided for each test result and for change from baseline by visit. Multiple measurements taken during the visit for a patient will be presented by the most severe value as noted in Section 8.7.3.1. For all chemistry analyses, the most severe could be in either direction for glucose, potassium, sodium, calcium, and magnesium. For these analytes, if within the normal limits, the value closest to the normal limits (either direction) is selected. If outside the normal limits, the value most distant from the normal limits (either direction) will be used.

A by-patient listing will be provided and will flag values outside of the reference range for each lab variable.

8.7.3.3. Urinalysis

A by-patient listing will be provided and will flag values outside of the reference range for each lab variable. Parameters to be collected and displayed are blood glucose, ketones, leukocyte esterase, nitrites, and pH. Protein microscopic examination will be conducted if blood or protein is 2+ or higher.

8.7.3.4. Other Tests

Other tests will be listed including hepatitis B antigen, hepatitis C antibody, serum pregnancy (β -human chorionic gonadotropin) (in female patients of child-bearing potential only), HIV-1 antibody, and HIV-2 antibody.

8.7.3.5. CTCAE Coding of Laboratory Data

Where laboratory values are categorized into NCI CTCAE version 4.0 grades, the categories are defined according to the criteria available on the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Note that grades are applied based only on the numeric value of the parameter assessed; clinical signs and symptoms are not considered. For example, Grade 4 hyperglycemia will be assigned based solely on the value of the glucose measurement, and acidosis will not be considered. Where categories are only distinguished by clinical signs or symptoms, the lowest of the possible grades will be assigned that do not involve the clinical sign or symptom described. Grade 0 means normal.

NCI CTCAE grades will be applied for the following lab parameters (given in Appendix 2):

- Hematology: hemoglobin (anemia, hemoglobin increased), total WBC (leukopenia), lymphocytes (lymphopenia), neutrophils (neutropenia), and platelets (thrombocytopenia).

- Chemistry: albumin (hypoalbuminemia), alkaline phosphatase, ALT, AST, total bilirubin, calcium (hypocalcemia, hypercalcemia), creatinine, glucose (hyperglycemia, hypoglycemia), magnesium (hypermagnesemia, hypomagnesemia), phosphorus (hypophosphatemia), potassium (hyperkalemia, hypokalemia), and sodium (hyponatremia, hypernatremia).

A summary of maximum severity observed on-study for all parameters noted above will be generated for the coded hematology and chemistry parameters. Patients will only be included once, in the maximum severity, for each laboratory parameter. Additionally, a shift summary of baseline to maximum severity on-study will also be produced. Patients with at least 1 on-study measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present (baseline will be included as a missing category). Thus, percentages for each parameter will be based on the total number of patients with an on-study measurement for the parameter of interest.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0," which is defined as normal.

8.7.4. 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 derived according to the Fridericia formula

$$QT_{c\text{-}F} = QT / (RR - RR/1000)^{1/3}$$

as well as Bazett's formula

$$QT_{c\text{-}B} = QT / (RR - RR/1000)^{1/2}.$$

The descriptive statistics for the ECG parameters and changes from predose Day 1 will be summarized by dose cohort at each time point prior to the start of the maintenance phase, end of study and the maximum and minimum observed values on study.

The number and percent of patients with $QT_{c\text{-}F}$ values in the following ICH E14 categories will be summarized by dose cohort:

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

The similar table will be presented for $QT_{c\text{-}B}$.

The patients in the following categories will be presented in patient listings: overall, rhythm, conduction, morphology, myocardial infarction, and the presence of ST, T, and U wave abnormalities.

8.7.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

The following parameters of vital signs will be summarized through descriptive statistics by dose cohort at baseline (defined as the last observation prior to the 1st dose), at each posttreatment time point (defined as the day of dose injection but prior to study drug administration), and at the end of study: body temperature, respiration rate, pulse, blood pressure (diastolic and systolic), and weight. Changes from baseline will be summarized in the same manner.

Note that height will be converted to centimeter (cm), weight will be converted to kilogram (kg), and temperature will be converted to Celsius (C).

8.7.6. ECOG Performance Status

A summary of ECOG performance status over time will be presented through the end of the Maintenance Phase, at the end of treatment and for the maximum and minimum across all on-treatment data. The number and percentage of each level will be generated at each planned visit. In addition, a summary of the minimum and maximum status observed during the study will be included.

8.7.7. 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 first dose of the 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 and percent of patients using each concomitant medication will be summarized according to the World Health Organization (WHO) Drug Dictionary preferred name. Patients with multiple uses of a concomitant medication during a treatment period will be counted once for a given preferred name for the treatment period. Additionally, prior and concomitant medication data will be listed.
Prior and concomitant corticosteroid use will be listed. Corticosteroids will be identified by an answer of "Yes" to the CRF question "Is medication a corticosteroid?".

9. REFERENCES:

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10. Appendix 1 Laboratory Standard Units

Laboratory Test	SI Unit
Albumin	g/L
Alkaline Phosphatase	U/L
Bands	10^9/L
Basophils	10^9/L
Bicarbonate	mmol/L
Bilirubin (Direct, Indirect, Total)	μmol/L
Blood Urea Nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
Creatinine	μmol/L
Eosinophils	10^9/L
Glucose	mmol/L
Hematocrit	frac of 1
Hemoglobin	g/L
Lactate Dehydrogenase	U/L
Lymphocytes	10^9/L
Atypical Lymphocytes	10^9/L
Magnesium	mmol/L
Mean Corpuscular Hemoglobin	pg
Mean Corpuscular Hemoglobin Conc	g/L
Mean Corpuscular Volume	fL
Monocytes	10^9/L
Myeloblasts	10^9/L
Nucleated RBC	10^9/L
Segmented Neutrophils	10^9/L
Total Neutrophils	10^9/L
Phosphorous	mmol/L
Platelets	10^9/L
Potassium	mmol/L
Total Protein	g/L
Prothrombin Time	s
Partial Thromboplastin Time	s
Red Blood Cells	10^{12}/L
Sodium	mmol/L
Aspartate Transaminase	U/L
Alanine Transaminase	U/L
Sodium	mmol/L

Uric Acid	umol/L
White Blood Cells	10^9/L

11. Appendix 2 CTCAE v4.0 grading for laboratory values and QTc

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 × 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10^9 /L	<1000/mm^3; <1.0 × 10^9/L
Investigations	Hemoglobin increased	>0 - 2 gm/dL above ULN or above baseline, if baseline is above ULN	>2 - 4 gm/dL above ULN or above baseline, if baseline is above ULN	>4 gm/dL above ULN or above baseline, if baseline is above ULN	-
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Investigations	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x10^9 /L	<800 - 500/mm^3; <0.8 - 0.5 × 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 × 10^9 /L	<200/mm^3; <0.2 × 10^9 /L
Investigations	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 × 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 × 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 × 10^9/L	<500/mm^3; <0.5 × 10^9/L
Investigations	Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 × 10^9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 × 10^9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 × 10^9/L	<25,000/mm^3; <25.0 × 10^9/L
Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Alkaline phosphatase increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Alanine aminotransferase increased	>ULN - 3.0 × ULN	Asymptomatic with ALT >3.0 - 5.0 × ULN; >3 × ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia	>5.0 - 20.0 × ULN; >5 × ULN for >2 wks	>20.0 × ULN
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	Asymptomatic with AST >3.0 - 5.0 × ULN; >3 × ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia	>5.0 - 20.0 × ULN; >5 × ULN for >2 wks	>20.0 × ULN

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Blood bilirubin (total) increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Metabolism and nutrition disorders	Hypercalcemia	>ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypocalcemia	<LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	<8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
Investigations	Creatinine increased	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 baseline; >3.0 - 6.0 × ULN	>6.0 × ULN

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Electrocardiogram QT corrected interval prolonged		QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms	

Note: Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0", which is defined as normal.