Nektar Therapeutics

CLINICAL STUDY PROTOCOL

A PHASE 1/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION AND DOSE EXPANSION STUDY OF NKTR-214 IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMOR MALIGNANCIES

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INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies
PROTOCOL NUMBER:	15-214-01
PHASE OF STUDY:	Phase 1/2
PROTOCOL DATE:	12 August 2015
STUDY SPONSOR:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

LIST OF STUDY CONTACTS

Study Contact	Name	Contact Information
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ALP	alkaline phosphatase
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
BOR	best overall response
CBR	clinical benefit rate
CD8T	tumor killing CD8+ T cell
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCI	data collection instrument
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOA	end of administration
EOT	end of treatment
EMA	European Medicines Agency
ET	early termination

Abbreviation or Term	Definition
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hr	hour(s)
ICF	informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IEC	independent ethics committee
IL-2	interleukin-2
IL2Rα	IL-2 receptor alpha subunit
IL2Rβ	IL-2 receptor beta subunit
IND	Investigational New Drug
irAE	immune-related adverse event
IRB	institutional review board
IV	intravenous
kg	Kilogram
LDH	lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAD	maximum administered dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Term	Definition
min	minute(s)
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death protein 1
PEG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
q14d	every 14 days
q21d	every 21 days
q28d	every 28 days
QTcF	Fridericia's corrected QT interval
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	Recombinant human interleukin 2
RP2D	recommended Phase 2 dose

Abbreviation or Term	Definition
SAE	serious adverse event
SD	stable disease
SLD	sum of the longest diameters
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination phase half-life
TTE	transthoracic echocardiogram
T_{max}	time to maximum concentration
Treg	regulatory T cell
TEAE	treatment emergent adverse event
TTR	time to response
ULN	upper limit of normal
USP	United States Pharmacopeia
TIL	tumor-infiltrating lymphocyte
V_d	volume of distribution

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Product:	NKTR-214 drug product
Name of Active Ingredient:	NKTR-214 drug substance
Title of Study:	A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies
Duration of Treatment:	Subjects will be treated until unacceptable toxicity, or disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (treatment may continue if there is clinical benefit as determined by the Investigator).
Phase of Development:	Phase 1/2
Objectives:	The primary objectives are: • To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) of NKTR-214 • To evaluate the efficacy of NKTR-214 by assessing the objective response rate (ORR) at the MTD or the dose below the MTD The secondary objectives are: • To evaluate the efficacy of NKTR-214 by assessing best overall response (BOR), [redacted] duration of response (DOR), clinical benefit rate (CBR), time to response (TTR), [redacted] • To characterize the pharmacokinetic (PK) profile of NKTR-214 and relevant metabolites • To assess the immunogenicity of NKTR-214 The exploratory objectives are: • To assess the immunologic effect of NKTR-214 in tumor tissue on tumor-infiltrating lymphocytes (TIL) • To assess the immunologic effects of NKTR-214 in blood, including effects on cytokines, natural killer (NK) cells, T-cells, and other serum proteins and immune modulators
Study Population	Adults age 18 and older with histologically confirmed locally advanced or metastatic solid tumors in Part 1 (Dose Escalation) and renal cell carcinoma (RCC) in Part 2 (Dose Expansion) who have measurable disease
Number of Subjects (planned):	Part 1: Approximately 50 subjects will be enrolled into the dose escalation phase of the study. Part 2: Approximately 50 subjects will be enrolled into the dose expansion phase of the study.
Number of Study Sites:	Approximately 3 clinical study sites for dose escalation cohorts; up to 15 additional sites may be added for the dose expansion cohort.
Countries:	USA

Study Design:

This is a Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-214 in subjects with locally advanced or metastatic solid tumor malignancies. The study will be conducted in 2 parts: Part 1, Dose Escalation and Part 2, Dose Expansion.

Part 1: Sample Dose Escalation Scheme

Cohort	NKTR-214 Dose
Cohort 1	0.003 mg/kg
Cohort 2	0.006 mg/kg
Cohort 3	0.012 mg/kg
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The Sponsor and at least one Investigator will jointly decide the following:

- Dose levels for a given cohort may be reduced by 25-50% depending on the severity, duration and frequency of toxicities observed at the previous dose level as well as the pharmacokinetic (PK) profile, if available.
- In the event that MTD is not determined at the highest dose level listed in the table, dose escalation at no more than 100% higher than previous dose may continue.
- The schedule of dosing can be modified to every 14 days or every 28 days based on a review of the safety data and available PK data.
- Once the MAD has been reached, lower doses and different dose schedules may be assessed, within the anticipated total number of subjects of approximately 50.

Dose escalation will proceed as follows for each dose level:

Number of Subjects with a dose-limiting toxicity (DLT) at a Given Dose Level	Dose Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next higher dose level.
1 out of 3	Enter at least 3 more subjects at the current dose level. If 0 of these 3 additional subjects experience DLT, proceed to the next higher dose level. If 1 or more of this group suffers a DLT, then the dose escalation is stopped, and this dose is declared the maximum administered dose (MAD). Three (3) additional subjects will be entered at a lower dose level if only 3 subjects were treated previously at that dose.
≥ 2	Dose escalation will be stopped. This dose level will be declared the MAD. Three (3) additional subjects will be entered at a lower dose level if only 3 subjects were treated previously at that dose.

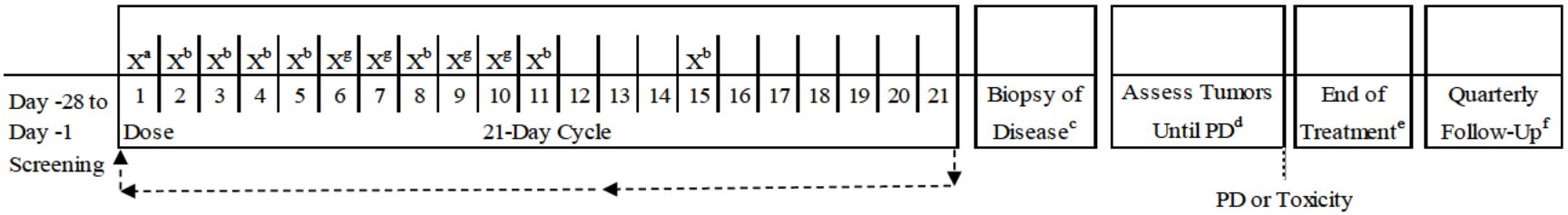
	<table><tr><td>≤ 1 out of 6 at highest dose level below the maximally administered dose</td><td>This is the MTD. At least 6 subjects must be entered at this dose level before declaring it as the dose for part 2 dose expansion.</td></tr></table> For each dose escalation cohort, the first subject enrolled to the cohort will be treated on Cycle 1 Day 1 and monitored for tolerance through Cycle 1 Day 5 prior to dosing of the additional subjects at that dose level. Safety data from Cycle 1 will be utilized to assess dose escalation for each new cohort. A DLT is defined as a Grade 3 or higher study-drug-related or possibly related adverse event (AE) occurring within the first cycle of dosing (excluding Grade 3/4 transient lymphopenia < 14 days in duration, tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor, a transient, reversible ≤ grade 3 infusion AE (< 24 hours), non-clinically significant laboratory abnormalities, or fatigue lasting less than 72 hours) using National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 4.03. **Part 2: Dose Expansion** Enrollment into the renal cell carcinoma cohort may commence once the MTD or RP2D has been determined. Subjects in the dose expansion cohort will be treated every 21 days (q21d), every 14 days (q14d), or every 28 days (q28d) until tumor progression (treatment may continue if there is clinical benefit as determined by the Investigator), death, unacceptable toxicity, symptomatic deterioration, achievement of maximal response, subject's choice, the Investigator's decision to discontinue treatment, the subject withdraws consent or Nektar Therapeutics decides to terminate the trial.
Key Inclusion Criteria:	**For Parts 1 and 2:** • Willing and able to provide written informed consent. • Histologically confirmed diagnosis of a locally advanced (not amenable to curative therapy such as surgical resection) or metastatic solid tumor. • Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF). • Life expectancy > 12 weeks. • Patients must not have received interleukin-2 [IL-2] therapy within 12 months of Cycle 1 Day 1. • Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. • Measurable disease per RECIST version 1.1. **For Part 2 only:** Renal Cell Carcinoma (RCC) a. Histologically confirmed diagnosis of unresectable or metastatic RCC with predominantly clear cell elements. b. Must have received only 1 prior line of anti-angiogenic therapy c. Must not have received prior immunotherapy with immune-modulators including but not limited to checkpoint inhibitors such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody and any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways, indoleamine 2,3-dioxygenase pathway inhibitors, cancer vaccines, adoptive cell therapies, and cytokine therapies.

Test Product, Dose and Mode of Administration:	NKTR-214; Starting dose of 0.003 mg/kg intravenous (IV) infusion administered over 15 (± 5) minutes q21d
Safety:	Assessment of safety will be determined by an ongoing review of the following: • incidence of AEs, including serious AEs (SAEs) • clinical laboratory tests (blood and urine sampling) • vital signs • electrocardiograms (ECG) and echocardiograms • physical examination
Pharmacokinetics:	Blood samples for PK analyses will be collected from all subjects enrolled in the dose escalation and dose expansion phases. Serial PK samples will be collected at multiple scheduled time points. Plasma concentrations of NKTR-214 and its metabolites will be measured for each plasma PK sample using validated method(s). Pharmacokinetic parameters such as maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), clearance (CL), volume of distribution (V_d), and half-life ($t_{½}$) will be estimated from plasma concentration-time data where possible.
Pharmacodynamics:	Systemic and tumor tissue based pharmacodynamic effects of NKTR-214 will be examined. Blood samples for systemic pharmacodynamic analyses will be collected pre- and post-NKTR-214 treatment from all subjects enrolled to assess the effects of NKTR-214 on markers of immune system activation, cytokines and immune cell populations. Fresh tumor tissue will be collected pre- and post-NKTR-214 treatment in consenting subjects for characterization of TILs, and immune system-related genes and proteins. In addition, archival tumor tissue samples will be collected from all subjects for analysis of immune system-related genes and proteins.
Efficacy:	Tumor measurements will be performed every 8 weeks ± 7 days. The primary efficacy measurement will be objective response rate (ORR) by tumor type. ORR by dose group will be descriptively presented. Other efficacy outcomes will include: • best overall response (BOR) • [redacted] • duration of response (DOR) • clinical benefit rate (CBR) • time to response (TTR) • [redacted] • tumor markers (e.g., LDH in melanoma) as an exploratory endpoint
Statistical Methods:	**Safety:** The primary safety analyses will include incidence of DLTs by dose cohort. Safety analyses will summarize the incidence, grade and duration of toxicities according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE), version 4.03. All AEs will be listed and tabulated by system organ class, preferred term, and coded according to the Medical Dictionary for Regulatory Activities

	(MedDRA). The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. Vital signs (including change in weight) and clinical laboratory test results will be listed and summarized descriptively by dose (for the dose escalation phase) and by tumor type (for the dose expansion phase). Any significant physical examination findings will be listed. ECG data will be evaluated by central review. Abnormalities, if present, will be listed. A separate listing and summary of all immune-related AEs (irAEs) will be provided. **Efficacy:** Efficacy assessments will be summarized separately for the dose escalation and dose expansion cohorts. In order to assess preliminary efficacy, the primary efficacy outcome measurement ORR, and the secondary efficacy outcomes, BOR, CBR, and TTR, will be tabulated by dose and tumor type. [redacted] Individual tumor measurements, tumor size and percent changes in tumor size will be listed. Changes in tumor size will be presented graphically for each specific tumor type. ORR and BOR will each be estimated based on the response evaluable population which is defined as subjects with measurable disease at baseline who receive the study drug and also have one post-baseline assessment of tumor response or are withdrawn due to progressive disease/death prior to first response assessment. DOR will be estimated for subjects who achieve complete response (CR) or partial response (PR). Other secondary efficacy analyses will be based on the all treated population and may be done for the response evaluable population as sensitivity analyses. Pharmacokinetic parameters will be tabulated and summarized with descriptive statistics by dose level. Values for biomarker expression will be calculated at each observation time. Changes in expression from screening to each observation time will be assessed.

1.1 Study Schematic

Figure 1: Study Schematic – Dose Escalation



a. Pre-treatment safety assessments will occur on Day 1 of each cycle. Pre-treatment biopsy of a non-target lesion will be performed prior to Cycle 1, Day 1. Study drug will be given as a 15-minute (± 5 minute) intravenous infusion.

b. Safety and PK assessments will occur in-clinic on Days 1-5, 8, 11, and 15 of Cycles 1 and 2. In-clinic visits to assess safety and PK will occur only on Day 8 of all other cycles.

c. Biopsy of a non-target lesion will be performed at Week 3 (7 to 1 days prior to Cycle 2, Day 1) unless tumor is inaccessible. Additional biopsies may be performed at the time of progression. Pre- and post-treatment biopsies should be taken from the same lesion, if feasible.

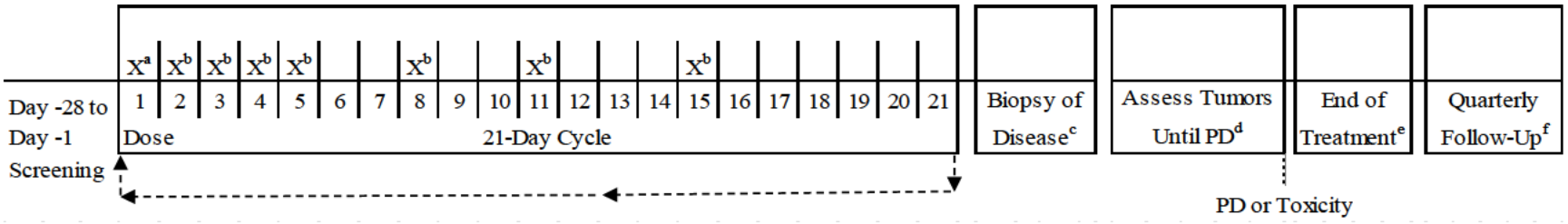
d. Disease will be assessed every 8 weeks (± 7 days) from screening until documentation of progressive disease (PD) (treatment may continue if there is clinical benefit), withdrawal of consent or death.

e. End of Treatment visit will occur 30 days (+ 10 days) after the last dose of study drug.

f. Every three months (±7 days) following the End of Treatment Visit, subjects will be contacted to assess progression via RECIST (if not determined during study treatment), receipt of subsequent anti-cancer therapy, and resolution of all toxicity attributable to study drug.

g. Vital signs will be assessed on Days 6, 7, 9, and 10 of Cycles 1 and 2 either in-clinic or using home health care visits.

Figure 2: Study Schematic – Dose Expansion



a. Pre-treatment safety assessments will occur on Day 1 of each cycle. Pre-treatment biopsy of a non-target lesion will be performed prior to Cycle 1, Day 1. Pre-treatment stool sample will be collected prior to Cycle 1, Day 1. Study drug will be given as a 15-minute (± 5 minute) intravenous infusion.

b. Safety and PK assessments will occur in clinic on Days 2, 3, 4, 5, 8, 11, and 15 of Cycles 1 and 2. In-clinic visits to assess safety and PK will occur only on Day 8 of all other cycles.

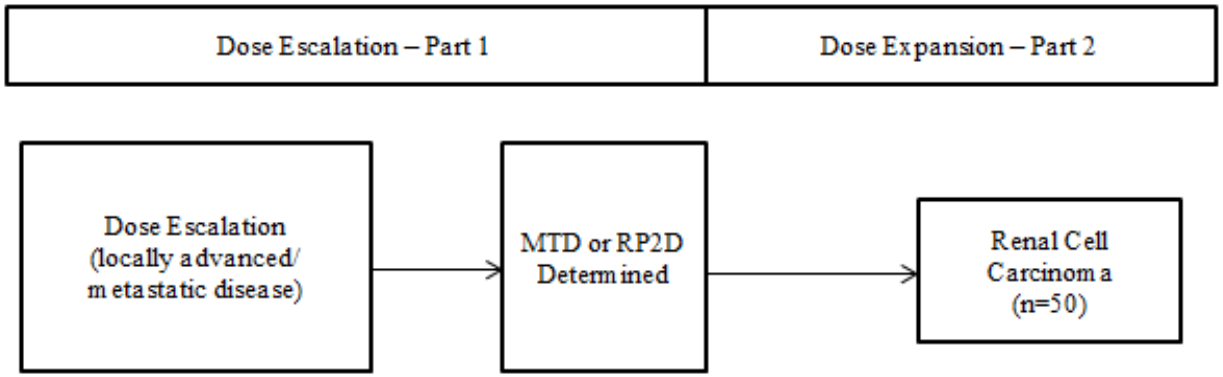
c. Biopsy of a non-target lesion will be performed at Week 3 (7 to 1 days prior to Cycle 2, Day 1) unless tumor is inaccessible. There is 1 optional biopsy at the time of progression. Pre- and post-treatment biopsies should be taken from the same lesion, if feasible.

d. Disease will be assessed every 8 weeks (± 7 days) from screening until documentation of progressive disease (PD) (treatment may continue if there is clinical benefit), withdrawal of consent or death.

e. End of Treatment visit will occur 30 days (+ 10 days) after the last dose of study drug.

f. Every three months (± 7 days) following the End of Treatment Visit, subjects will be contacted to assess progression via RECIST (if not determined during study treatment), receipt of subsequent anti-cancer therapy, and resolution of all toxicity attributable to study drug.

Figure 3: Study Schematic



1.2 Schedule of Assessments

Table 1: Schedule of Visits and Procedures Dose Escalation (Phase 1)

Assessment Period	Screening	Cycle 1 and Cycle 2													Cycle 3 and Beyond			Post-treatment	
Study Days[a]	Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 15	Day 22b	Day 1	Day 8	Day 22[b]	End of Treatment (+10 days)	Follow-up 3 mo
Informed consent[c]	X																		
Inclusion/exclusion criteria	X	X																	
Demographics	X																		
Medical/cancer history[d]	X																		
Medication history[e]	X																		
Physical examination[f]	X	X	X	X	X	X			X			X	X[g]	X	X	X	X	X	
Vital signs[h]	X	X	X	X	X	X	X[i]	X[i]	X	X[i]	X[i]	X	X[g]	X	X	X	X	X	
ECOG performance status	X															X			
ECG[j]	X	X	X	X	X	X			X			X	X[g]	X	X	X	X	X	
ECHO[k]	X																	X	
Pregnancy test[l]	X	X													X			X	
Hematology[m]	X	X	X	X	X	X			X			X	X[g]	X	X	X	X	X	
Serum chemistry[n]	X	X			X				X			X	X[g]	X	X	X	X	X	

Table 1: Schedule of Visits and Procedures Dose Escalation (Phase 1) (Cont'd)

Assessment Period	Screening	Cycle 1 and Cycle 2													Cycle 3 and Beyond			Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 15**	**Day 22b**	**Day 1**	**Day 8**	**Day 22**[b]	**End of Treatment (+10 days)**	**Follow-up 3 mo**
Coagulation[o]	X	X			X				X			X	X[g]	X	X	X	X	X	
Additional labs[p]	X												X[g]		X[p]			X	
Urinalysis (dipstick)[q]	X	X													X			X	
Serology[r]	X																		
Archival tumor tissue collection[s]	X																		
Tumor biopsy if accessible[t]	X[t]	X[t]													X[t]			X[t]	
Immunogenicity serum sample collection	X	X[u]													X[u]			X	X
Tumor assessment[v]	X														Every 8 weeks (± 7d)			X	
AEs[w]		←												→				X	
Concomitant medications	X	←												→				X	
Biomarker blood sample collection		X[x]							X[x]						X[x]			X[x]	
PK blood sample[y,z]		X	X	X	X	X			X			X	X[g]		X	X		X	

Table 1: Schedule of Visits and Procedures Dose Escalation (Phase 1) (Cont'd)

Assessment Period	Screening	Cycle 1 and Cycle 2													Cycle 3 and Beyond			Post-treatment	
Study Days[a]	Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 15	Day 22b	Day 1	Day 8	Day 22[b]	End of Treatment (+10 days)	Follow-up 3 mo
Administer fluids and advise patients[aa]		X	X	X	X	X									Days 1-5				
NKTR-214 administration[bb]		X													X				
Quarterly follow-up																			X

Footnotes:

a. The acceptable visit window is + 1 days for Day 11 and ±1 day for Day 8 and Day 15 and ± 7 days for the follow-up visit post-treatment. Visits may be skipped or postponed if prospectively identified by the Investigator (e.g., national holidays, subject vacations). If Day 4 visit is missed then Day 4 assessments must be done at the next in-clinic visit. All procedures and examinations should be performed before the administration of study drug(s), except as indicated below.

b. Assessments only applicable if dosing cycle is changed to 28-day cycle.

c. The Institutional Review Board (IRB)-approved informed consent form (ICF) must be signed before any study-specific procedures or examinations are performed.

d. An event occurring after the subject has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator OR there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any new or clinically significant changes in the subject's medical and/or cancer history that occur immediately after the first dose of drug will be recorded as AEs.

e. Include prior cancer treatments: previous immunotherapy, chemotherapy, targeted therapy, radiation, OTC medications, herbs and dietary supplements.

f. Physical examinations at screening/baseline, at day 1 of each cycle, and at end of treatment should be complete assessments (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the subject's clinical symptoms. Weight is to be reported at each visit, height at screening/baseline visit only.

g. Assessments not applicable if dosing cycle is changed to 14-day cycle.

h. Vital signs include temperature, pulse, respiration, systolic and diastolic blood pressure, and oxygen saturation. On dosing days, monitor the subject for 1 hour postdosing and record vital signs at the end of the hour. However, if the subject experienced a Grade ≥ 2 infusion-related reaction or hypotension during the study drug administration, the patient may be monitored for 24 hours per clinical judgment. Per clinical judgment, additional monitoring might be implemented for subsequent cycles.

i. Vital signs will be assessed on days 6, 7, 9, and 10 of Cycles 1 and 2 either in-clinic or using home health care visits.

j. A 5-minute summary ECG will be performed for all subjects at screening and during the 5 minutes prior to the time points of predose, 0.5 hr ± 5 min, 3 hr ± 10 min, 6 hr + 2 hr on Day 1 of Cycles 1 and 2 and on Days 2, 3, 4, 5, 8, 11, and 15 of Cycles 1 and 2. A 5-minute summary ECG starting 5 minutes before the predose timepoint will be performed on Days 1 and 8 of Cycle 3 and beyond, including End of Treatment (EOT). Frequency of ECGs may be increased if clinically indicated. Prior to performing ECGs, subjects should rest in the supine position for at least 5 minutes. All ECGs should be taken prior to the PK draw.

k. Stress echocardiogram (either exercise or nuclear) will be performed for all subjects within 60 days prior to Cycle 1 Day 1 and at EOT to assess for cardiac function and left ventricular ejection fraction (LVEF). At the discretion of the Investigator, patients who are unable to perform a stress echocardiogram may instead have a multigated acquisition (MUGA) scan or transthoracic echocardiogram (TTE). The same assessment method should be used for the same subject throughout the study.

l. For women of childbearing potential, serum β-HCG pregnancy test is required at screening. Urine or serum pregnancy tests to be performed on Day 1 of each subsequent cycle and EOT. A pregnancy test does not need to be performed on women who are postmenopausal for at least 1 year or surgically sterile for at least 3 months before signing the ICF.

m. Hematology performed at the indicated times by local laboratory: red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), platelet count, white blood cell (WBC) count, and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) (**Appendix 1**). If hematology demonstrates CTCAE grade 3/4 cytopenias, increase frequency to daily monitoring as clinically appropriate. Hematology assessments scheduled for the day of study drug dosing must be available and assessed for toxicity before dosing. The sampling for hematology assessment can be drawn up to 24 hours prior to dosing.

n. Serum chemistry performed at the indicated times by local laboratory: sodium, potassium, calcium, chloride, creatinine, calculated creatinine clearance (Cockcroft-Gault), total bilirubin, albumin, alkaline phosphatase, CO2 or bicarbonate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, blood urea nitrogen (BUN), total protein (TP), gamma-glutamyl transferase (GGT), and uric acid (**Appendix 1**).

o. Coagulation performed at the indicated times by local laboratory: partial thromboplastin time and prothrombin time (**Appendix 1**).

p. Additional tests performed at Screening, on Day 15 of Cycle 1 and 2, and at End of Treatment: thyroid stimulating hormone, lipase, amylase, free thyroxine (T4), creatine kinase, HLA typing (only at screening) and on Day 1 beginning from Cycle 4 (**Appendix 1**).

q. Microscopy is required only to follow-up clinically significant urine dipstick findings. List pH, specific gravity, protein, glucose, ketones, bilirubin, blood, and leukocyte esterase (**Appendix 1**).

r. Serology tests include hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), and human immunodeficiency virus (HIV) antibody (**Appendix 1**).

s. Unstained formalin-fixed, paraffin embedded, archival tumor tissue sections on slides are acceptable.

t. One pre-treatment tumor tissue biopsy will be collected during screening (Cycle 1 Day 1 to 28 days). If a pre-treatment biopsy was collected within 28 days, tumor sections can be provided. One on-treatment tumor tissue biopsy will be collected at Week 3 (7 to 1 days prior to Cycle 2 Day 1). An additional tumor tissue biopsy may be collected at the time of progression. All tumor biopsies will be collected from the same non-target lesion, if feasible. Exceptions will be made with Medical Monitor approval for tumors that are inaccessible.

u. The screening immunogenicity sample should be drawn within 14 days prior to Day 1 Cycle 1. No immunogenicity sample will be drawn at pre-dose on Cycle 1 Day 1. Immunogenicity samples will be drawn at pre-dose on Cycle 2 Day 1, pre-dose on Day 1 of all odd-numbered cycles thereafter (e.g., Cycles 3, 5, 7, etc.), and at End-of-Treatment and Follow-up.

v. Tumor assessment at screening then every 8 weeks (± 7 days) and End-of-Treatment (unless scan done within 4-weeks). To ensure comparability, the baseline radiographs/scans and subsequent radiographs/scans to assess response should be performed using identical techniques. In the event of a partial response (PR) or complete response (CR), confirmatory radiographic imaging should be completed at least 4 weeks from imaging showing a CR or PR. If the subject discontinues treatment for a reason other than Progressive Disease, imaging will be conducted every 3 months until progressive disease is noted or start of new treatment.

w. Any new or clinically significant changes in the subject's medical and/or cancer history that occur immediately after the first dose of drug will be recorded as AEs. All AEs, including serious AEs (SAEs), will be recorded immediately after the first dose of study drug until 30 days after the last dose of study medication. An SAE related to study procedures or study conduct must be reported to Nektar Therapeutics if it occurs prior to first dose of study drugs. SAEs must be reported as described in Section 8.7 of the protocol. Treatment-related AEs ongoing at the post-treatment visit should be followed to resolution or until the Investigator considers them "chronic" or "stable".

x. Biomarker sample will be drawn prior to dose on Day 1 and on Day 8 ± 3 days. In addition, biomarker samples will be collected prior to dose on Day 1 of Cycle 3 and all odd-numbered cycles thereafter (e.g., Cycles 3, 5, 7, etc.). If the optional tumor biopsy at disease progression is collected, collect an additional biomarker sample at the same time.

y. Blood samples (2 mL) for PK analyses will be collected in all cycles, with more intense sampling in Cycles 1 and 2. PK sample times are as follows: Cycle 1 and Cycle 2 Day 1: predose, end of administration (EOA ± 2 min), 0.5 hr ± 5 min, 3 hr ± 10 min, 6 hr + 2 hr, and 2, 3, 4, 5, 8, 11, and 15 days postdose. Cycle ≥3: predose, EOA (± 2 min), Day 8, and End of Treatment. On Days 2 and 3 of Cycles 1 and 2, 4 mL of blood will be drawn instead of the usual 2 mL. The blood draws should occur as close to 30 or 38 hours post dose as possible.

z. In the event of a possible study-drug-related SAE throughout the study, additional PK blood samples may be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.

aa. Administer at least 2 liters of fluid (IV or self-administered orally [e.g., fluid containing electrolytes]) for Days 1 to 5 of every cycle. Advise subjects to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 5 of every cycle. A Patient Wallet Card is available that contains important safety information.

bb. Administer NKTR-214 at the subject's assigned dose level as an intravenous infusion over 15 minutes ± 5 minutes.

Table 2: Schedule of Visits and Procedures Dose Expansion (Phase 2)

Assessment Period	Screening	Cycle 1 and Cycle 2									Cycle 3 and Beyond			Post-Treatment	
Study Days[a]	Day -28 to 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 11	Day 15	Day 22[b]	Day 1	Day 8	Day 22[b]	End of Treatment (+10 days)	Follow-up 3 mo
Informed consent[c]	X														
Inclusion/exclusion criteria	X	X													
Demographics	X														
Medical/cancer history[d]	X														
Medication history[e]	X														
Physical examination[f]	X	X					X		X[g]	X	X	X	X	X	
Vital signs[h]	X	X	X	X	X	X	X	X	X[g]	X	X	X	X	X	
ECOG performance status	X											X			
ECG[i]	X	X	X	X	X	X	X	X	X[g]	X	X	X	X	X	
ECHO[j]	X													X	
Pregnancy test[k]	X	X									X			X	
Hematology[l]	X	X	X	X	X	X	X		X[g]	X	X	X	X	X	
Serum chemistry[m]	X	X			X		X		X[g]	X	X	X	X	X	
Coagulation[n]	X	X			X		X		X[g]	X	X	X	X	X	
Additional labs[o]	X								X[g]		X[o]			X	

Table 2: Schedule of Visits and Procedures Dose Expansion (Phase 2) (Cont'd)

Assessment Period	Screening	Cycle 1 and Cycle 2									Cycle 3 and Beyond			Post-Treatment	
Study Days[a]	**Day -28 to 1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 11**	**Day 15**	**Day 22[b]**	**Day 1**	**Day 8**	**Day 22[b]**	**End of Treatment (+10 days)**	**Follow-up 3 mo**
Urinalysis (dipstick)[p]	X	X									X			X	
Serology[q]	X														
Archival tumor tissue collection[r]	X														
Tumor biopsy if accessible[s]	X	X									X				
Immunogenicity serum sample collection	X	X[t]									X[t]			X	X
Tumor assessment[u]	X										Every 8 weeks (± 7d)			X	
AEs[v]		←	—	—	—	—	—	—	—	—	—	—	→	X	
Concomitant medications	X	←	—	—	—	—	—	—	—	—	—	—	→	X	
Biomarker blood sample collection		X[w]					X[w]				X[w]			X[w]	
Stool sample collection		X[x]													
PK blood sample[y,z]		X	X	X	X	X	X	X	X[g]		X	X		X	
Administer fluids and advise patients[aa]		X	X	X	X	X					Days 1-5				
NKTR-214 administration[bb]		X									X				
Quarterly follow-up															X

Footnotes:

a. The acceptable visit window is + 1 day for Day 11 and ±1 day for Day 8 and Day 15 and ± 7 days for the follow-up visit post-treatment. Visits may be skipped or postponed if prospectively identified by the Investigator (e.g., national holidays, subject holidays). If Day 4 visit is missed then Day 4 assessments must be done at the next in clinic visit. All procedures and examinations should be performed before the administration of study drug(s), except as indicated below.

b. Assessments only applicable if dosing cycle is changed to 28-day cycle.

c. The Institutional Review Board (IRB)-approved informed consent form (ICF) must be signed before any study-specific procedures or examinations are performed.

d. An event occurring after the subject has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator OR there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any new or clinically significant changes in the subject's medical and/or cancer history that occur immediately after the first dose of drug will be recorded as AEs.

e. Include prior cancer treatments: previous immunotherapy, chemotherapy, targeted therapy, radiation, OTC medications, herbs and dietary supplements

f. Physical examinations at screening/baseline, at day 1 of each cycle, and at end of treatment should be complete assessments (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the subject's clinical symptoms. Weight is to be reported at each visit, height at screening/baseline visit only.

g. Assessments not applicable if dosing cycle is changed to 14-day cycle.

h. Vital signs include temperature, pulse, respiration, systolic and diastolic blood pressure, and oxygen saturation. Monitor the subject for 1 hour postdosing and record vital signs at the end of the hour. If a subject should experience a Grade ≥ 2 infusion reaction or hypotension during study visit subject may be monitored for 24 hours. Per clinical judgment additional monitoring might be implemented.

i. A 5-minute summary ECG will be performed for all subjects at screening and during the 5 minutes prior to the time points of predose, 0.5 hr ± 5 min., 3 hr ± 10 min, and 6 hr + 2 hr on Day 1 of Cycles 1 and 2 and on Days 2, 3, 4, 5, 8, 11, and 15 of Cycles 1 and 2. A 5-minute summary ECG starting 5 minutes before the predose time point will be performed on Days 1 and 8 of Cycle 3 and beyond, including EOT. Frequency of ECGs may be increased if clinically indicated. Prior to performing ECGs, subjects should rest in the supine position for at least 5 minutes. All ECGs should be taken prior to the PK draw.

j. Stress echocardiogram (either exercise or nuclear) will be performed for all subjects within 60 days prior to Cycle 1 Day 1 and at End of Treatment to assess for cardiac function and left ventricular ejection fraction (LVEF). At the discretion of the Investigator, patients who are unable to perform a stress echocardiogram may instead have a MUGA scan or TTE. The same assessment method should be used for the same subject throughout the study.

k. For women of childbearing potential, serum β-HCG pregnancy test is required at screening. Urine or serum pregnancy tests to be performed on Day 1 of each subsequent cycle and EOT. A pregnancy test does not need to be performed on women who are postmenopausal for at least 1 year or surgically sterile for at least 3 months before signing the ICF.

l. Hematology performed at the indicated times by a central laboratory: red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), platelet count, white blood cell (WBC) count, and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) (**Appendix 1**). If hematology demonstrates CTCAE grade 3/4 cytopenias, increase frequency to daily monitoring as clinically appropriate. Hematology assessments scheduled for the day of study drug dosing must be available and assessed for toxicity before dosing. The sampling for hematology assessment can be drawn up to 24 hours prior to dosing.

m. Serum chemistry performed at the indicated times by a central laboratory: sodium, potassium, calcium, chloride, creatinine, calculated creatinine clearance (Cockcroft-Gault), total bilirubin, albumin, alkaline phosphatase, CO2 or bicarbonate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, blood urea nitrogen (BUN), total protein (TP), gamma-glutamyl transferase (GGT), and uric acid (**Appendix 1**).

n. Coagulation performed at the indicated times by a central laboratory: partial thromboplastin time and prothrombin time (**Appendix 1**).

o. Additional tests performed at screening, on Day 15 of Cycle 1 and 2, and at End of Treatment: thyroid stimulating hormone, lipase, amylase, free thyroxine (T4), creatine kinase, HLA typing (only at screening) and on Day 1 beginning from Cycle 4 (**Appendix 1**).

p. Microscopy is required only to follow-up clinically significant urine dipstick findings. List pH, specific gravity, protein, glucose, ketones, bilirubin, blood, and leukocyte esterase (**Appendix 1**).

q. Serology tests include hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), and human immunodeficiency virus (HIV) antibody (**Appendix 1**).

r. Unstained formalin-fixed, paraffin embedded, archival tumor tissue sections on slides are acceptable.

s. One pre-treatment tumor tissue biopsy will be collected during screening (Cycle 1 Day 1 − 28 days). If a pre-treatment biopsy was collected within 28 days, tumor section can be provided. One on-treatment tumor tissue biopsy will be collected at Week 3 (7 to 1 days prior to Cycle 2 Day 1). An additional tumor tissue biopsy may be collected at the time of progression. All tumor biopsies will be collected from the same non-target lesion, if feasible. Twenty tumor biopsies will be collected. Exceptions will be made with Medical Monitor approval for tumors that are inaccessible.

t. The screening immunogenicity sample should be drawn within 14 days prior to Cycle 1 Day 1. No immunogenicity sample will be drawn at pre-dose on Cycle 1 Day 1. Immunogenicity samples will be drawn at pre-dose on Cycle 2 Day 1, pre-dose on Day 1 of all odd-numbered cycles thereafter (e.g., Cycles 3, 5, 7, etc.), and at End-of-Treatment and Follow-up.

u. Tumor assessment at screening then every 8 weeks (± 7 days) and End-of-Treatment (unless scan done within 4-weeks). To ensure comparability, the baseline radiographs/scans and subsequent radiographs/scans to assess response should be performed using identical techniques. In the event of a partial response (PR) or complete response (CR), confirmatory radiographic imaging should be completed at least 4 weeks from imaging showing a CR or PR. If the subject discontinues treatment for a reason other than Progressive Disease, imaging will be conducted every 3 months until progressive disease is noted or start of new treatment.

v. Any new or clinically significant changes in the subject's medical and/or cancer history that occur immediately after the first dose of drug will be recorded as AEs. All AEs, including serious AEs (SAEs), will be recorded immediately after the first dose of study drug until 30 days after the last dose of study medication. An SAE related to study procedures or study conduct must be reported to Nektar Therapeutics if it occurs prior to first dose of study drugs. SAEs must be reported as described in Section 8.7 of the protocol. Treatment-related AEs ongoing at the post-treatment visit should be followed to resolution or until the Investigator considers them "chronic" or "stable".

w. Biomarker sample drawn prior to dose on Day 1 and on Day 8 ± 3 days. In addition, biomarker samples will be collected prior to dose on Day 1 of Cycle 3 and all odd-numbered cycles thereafter (e.g., Cycles 3, 5, 7, etc.). If the optional tumor biopsy at disease progression is collected, collect an additional biomarker sample at the same time.

x. Stool sample to be collected prior to Cycle 1 Day 1.

y. Blood samples (2 mL) for PK analyses will be collected in all cycles, with more intense sampling in Cycles 1 and 2. PK sample times are as follows: Cycles 1 and 2 Day 1: predose, end of administration (EOA ± 2 min), 0.5 hr ± 5 min, 3 hr ± 10 min, 6 hr + 2 hr, and 2, 3, 4, 5, 8, 11, and 15 days postdose. Cycle ≥ 3: predose, EOA ± 5 mins, Day 8 and End of Treatment.

z. In the event of a possible study drug-related SAE throughout the study, additional PK blood samples will be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.

aa. Administer at least 2 liters of fluid (IV or self-administered orally [e.g., fluid containing electrolytes]) for Days 1 to 5 of every cycle. Advise subjects to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 5 of every cycle. A Patient Wallet Card is available that contains important safety information.

bb. Administer NKTR-214 at the subject's assigned dose level as an intravenous infusion over 15 min ± 5 min.

2.0 INTRODUCTION

2.1 Background

Activating the immune system has the potential to produce durable responses in human cancers (**Hodi, 2010**). Recent attention in immunotherapy has focused on immune activation using checkpoint inhibitor antibodies (**Topalian, 2014**; **Robert, 2014**). However, direct immune stimulation using cytokines can also drive immune-mediated cancer cures (**Hanzly, 2014**). Aldesleukin directly stimulates the immune system and has been shown to lead to durable responses in ~10% of people with metastatic melanoma and renal cancer (**Payne, 2014**). However, in addition to aldesleukin acting as a stimulator of the immune system by activating tumor killing CD8+ T cells (CD8T), it also suppresses the immune system by activating regulatory T (Treg) cells (**Boyman, 2012**). Despite favorable clinical outcomes associated with aldesleukin, it has several therapeutic limitations including the need for inpatient hospital administration, 5 consecutive days of dosing, and the potential for serious toxicities, comprising capillary leak syndrome, hypotension and pulmonary edema requiring medical management in the intensive care unit.

A novel cytokine with optimized immune system activation and the targeted profile of NKTR-214 (i.e., a superior safety profile allowing for outpatient administration and a longer duration of action requiring less frequent dosing) would potentially be an important advancement for the treatment of patients with cancer. NKTR-214 consists of IL-2, which has the same amino acid sequence as aldesleukin, conjugated at a defined region within the protein to releasable polyethylene glycol (PEG) chains. The PEG chains render the molecule inactive. After administration in vivo, the PEG chains are slowly hydrolyzed to generate active cytokine conjugates. The most active IL-2 conjugates are the 2-PEG-IL2 and 1-PEG-IL2. Presumably, the location of the PEG chains on the active conjugated-IL-2 reduces the affinity to the IL2 receptor alpha subunit (IL2Rα), responsible for activating the undesirable Treg cells to a greater extent than the affinity to the IL-2-receptor beta subunit (IL2Rβ) relative to aldesleukin. In the tumor, NKTR-214 preferentially activates CD8+ T cells over Tregs. In addition, NKTR-214 provides sustained exposure to active 1-PEG and 2-PEG-IL2 in tumor.

2.2 Pre-clinical Data

2.2.1 Pharmacology

Pharmacology studies investigated the mechanism of action, as well as *in vitro* and *in vivo* activity of NKTR-214 using cell lines and syngeneic tumor models. After administration *in vivo*, PEG is slowly hydrolyzed from NKTR-214 to generate active conjugated IL-2 forms, 2-PEG-IL-2 and1-PEG-IL-2. Presumably, the location of the PEG chains on IL-2 interferes with the interaction to the receptor that activates the undesirable Treg cells in the tumor

(**Charych, 2013a**). As such, this receptor bias markedly increases the ratio of tumor killing CD8 T cells to Treg cells in tumors (to > 400) (**Charych, 2013b**). At the same time, the active conjugated IL-2 species released from NKTR-214 have different pharmacokinetic properties compared to aldesleukin, leading to a sustained and higher exposure in the tumor compared to an equivalent dose of aldesleukin (**Hoch, 2013**). NKTR-214, as a single agent, showed marked tumor growth suppression in the B16F10 mouse melanoma model, requiring a 10-fold lower cytokine equivalent dose that is administered once every 9 days, compared to twice daily dosing required for aldesleukin. The combinatorial immunity mediated by NKTR-214 induced CD8+ T cell activation and checkpoint blockade (anti-CTLA-4 and anti-PD-1) was synergistic, producing durable responses in multiple murine models of human cancer. Rechallenge and immune cell depletion studies assessing the anti-tumor activity induced by NKTR-214 combined with anti-CTLA-4 in the EMT6 murine breast tumor model demonstrated synergistic efficacy that was specific, durable, and dependent on both CD8T and NK cells. In all nonclinical species tested, NKTR-214 resulted in stimulation of several markers of immune system activation, in particular lymphocyte counts and sCD25.

2.2.2 Pharmacokinetics

Pharmacokinetic data in mice, rats, and monkeys demonstrated that a single dose of NKTR-214 provides sustained exposure to active conjugated IL-2 metabolites in both plasma and tumor. Exposure to NKTR-214 and active metabolites was consistent across nonclinical animal species. Active 2-PEG-IL-2 and 1-PEG-IL-2 are released gradually over 24 to 48 hours and decline in parallel to NKTR-214, at half-lives between 15-20 hours. No differences were observed between male and female animals, and accumulation was less than 2-fold after repeat administrations every 14 days. The NKTR-214 PK/ADME profile of gradual formation of and sustained tumor exposure to active 2-PEG-IL-2 and 1-PEG-IL-2 appears responsible for improved safety profile and antitumor activity in animals.

2.2.3 Toxicology

The safety of NKTR-214 was evaluated in rats and cynomolgus monkeys for up to 6 weeks of every 14 day (q14d) administration (q14dx3). A PEG control was included in the rat GLP toxicity study. Biomarkers of NKTR-214 immune stimulation (peripheral lymphocyte counts and plasma sCD25 levels) were included in these studies. In addition, cardiovascular safety was evaluated in a telemetry study in cynomolgus monkeys. The monkey was identified as the most sensitive species (see **Table 3**). In addition, NKTR-214 binding affinity to the IL-2 receptor and T-cell activation was comparable in vitro between human cell lines and the cynomolgus monkey cell lines. Clinical observations in the monkey after each NKTR-214 dose included transient (and reversible) hypoactivity, decreased appetite, emesis, diarrhea, decreased fecal output, and hunched posture on Days 2-9 after each dose. Findings consistent with systemic immune

stimulation included transient and dose-related increased white blood cell (WBC) counts, largely due to the increase in lymphocytes, and an increase in sCD25 that were observed 5 to 7 days post each NKTR-214 dose, all of which returned to baseline 14 days postdose. Noteworthy histopathology findings in the monkey were minimal to mild inflammation in multiple organs (including liver, heart, and kidney), hematopoiesis in bone marrow, and hypercellularity in the thymus and spleen. These histopathologic changes partially or in some cases completely resolved on recovery (6 weeks post last dose). Of note, no evidence of cardiovascular effects such as ECG abnormalities, hypotension, pulmonary edema or vascular leak were found in the monkey at the NKTR-214 maximum tolerated dose (MTD) of 0.1 mg/kg in contrast to the reports of vascular leak at the MTD for aldesleukin (**Anderson, 1993**). The MTD of NKTR-214 was determined as 0.3 mg/kg in rats and 0.1 mg/kg in monkeys. Detailed descriptions of these studies and their results can be found in the NKTR-214 Investigator's Brochure.

2.3 Starting Dose Rationale

The planned Phase 1 NKTR-214 starting dose of 0.003 mg/kg is $1/10^{th}$ of the cynomolgus monkey MTD (0.1 mg/kg) that has been corrected for body surface area. A dose of 0.003 mg/kg is expected to be active in humans since it is the lowest dose tested in the monkey toxicology study at which increases in both sCD25 (10-fold) and lymphocyte counts (2-fold) were observed. A dosing schedule of q21d was chosen for the first in human study based on the histopathologic changes (inflammatory cell infiltrates) in monkeys 14 days after administration of the last q14d NKTR-214 dose that almost completely resolved with an additional 4 weeks of recovery (6 weeks following the last dose). **Table 3** shows the safety margins for the proposed clinical starting dose of NKTR-214.

Table 3: Safety Margins for the Proposed Clinical Dose of NKTR-214

Toxicity Study	Animal MTD (mg/kg)	HED (mg/kg)[a]	Safety Margin	Phase 1 Starting Dose (mg/kg)
6-week Rat (q14dx3)	0.3	0.05	17	0.003
6-week Monkey (q14dx3)	0.1	0.03	10	

a. HED (Human Equivalent Dose) = (dose in animals)/(conversion factor). Conversion factor = 3.1 for monkeys and 6.2 for rats, based on body surface area differences per "FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." All NKTR-214 dose levels are expressed in IL-2 equivalents.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objectives are:

- To evaluate the safety and tolerability, and define the MTD of NKTR-214.
- To evaluate the efficacy of NKTR-214 by assessing the objective response rate (ORR) at the MTD or the dose below the MTD.

3.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of NKTR-214 by assessing best overall response (BOR), [redacted] duration of response (DOR), clinical benefit rate (CBR), time to response ([redacted]
- To characterize the pharmacokinetic (PK) profile of NKTR-214 and relevant metabolites.
- To assess the immunogenicity of NKTR-214.

3.3 Exploratory Objectives

The exploratory objectives are:

- To assess the immunologic effect of NKTR-214 in tumor tissue on tumor-infiltrating lymphocytes (TIL).
- To assess the immunologic effects of NKTR-214 in blood, including effects on cytokines, NK cells, T-cells, and other serum proteins and immune modulators.

4.0 STUDY DESIGN

4.1 Summary of Study Design

This study is a multicenter Phase 1/2, open-label, dose escalation and dose expansion study of NKTR-214 in subjects with histologically confirmed locally advanced or metastatic solid tumors who have measurable disease. The study will be conducted in 3 parts (Part 1 Dose Escalation followed by Part 2 Dose Expansion).

4.1.1 Screening

Up to 28 days.

4.1.2 Open-label Treatment

4.1.2.1 Part 1: Dose Escalation

Subjects will be enrolled in groups of at least 3 subjects in each cohort during the dose escalation phase.

The first dose to be studied will be 0.003 mg/kg administered as an IV infusion over 15 (± 5) minutes every 21 days (q21d). Dose escalation will be carried out as listed in **Table 5**. Dose levels for a given cohort, as listed in **Table 4**, may be reduced by 25-50% depending on the severity, duration and frequency of toxicities as well as the PK profile, if available, observed at the previous dose level. A subject's dose level may not be escalated once assigned.

For each dose level, the first subject enrolled will be dosed on Cycle 1 Day 1 and monitored for safety and tolerability on Cycle 1, Days 1 through 5, before additional subjects are dosed.

In situations where a cohort of 3 subjects has been enrolled and additional subjects in screening have been deemed eligible for the study, these additional eligible subjects may be enrolled to the cohort. In the event of more than 3 subjects being enrolled to a cohort, the dose escalation decision will be made when the first 3 subjects in the cohort have completed their first cycle (i.e. completion of cycle or occurrence of a dose-limiting toxicity [DLT]). Moreover, the cohort safety review committee or Sponsor may determine that inadequate information has been obtained in a cohort of 3 subjects and to further understand the benefit/risk profile at a given dose level, additional subjects may be enrolled.

Additional subjects may be enrolled at other doses and frequencies deemed to be safe to more fully explore the safety, tolerability, pharmacokinetics, biomarker assessments, and preliminary efficacy of NKTR-214. These additional cohorts of up to 12 subjects may be enrolled to further evaluate NKTR-214 at the recommended phase 2 dose or at doses at or below the MTD.

During dose escalation, subjects who are withdrawn from the study during Cycle 1 for reasons other than occurrence of a DLT will be replaced.

A DLT is defined as a Grade 3 or higher study drug-related or possibly related AE occurring within the first cycle of dosing (excluding Grade 3/4 transient lymphopenia < 14 days in duration, tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor, a transient, reversible ≤ grade 3 infusion AE [< 24 hours], non-clinically significant laboratory abnormalities, or fatigue lasting less than 72 hours) using National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 4.03.

All drug related AEs after Cycle 1 will continue to be collected and evaluated by the Investigators and the Sponsor on an ongoing basis and may be taken into consideration in determining the MTD.

Dose Escalation Scheme

For each dose level, the first subject enrolled to the dose cohort will be treated and monitored from Cycle 1, Day 1 through Cycle 1, Day 5 for tolerance prior to the dosing of additional subjects at that dose level. The first subject enrolled to the study will be administered NKTR-214 at the first dose level of 0.003 mg/kg (**Table 4**). Enrollment into the next cohort cannot begin until a full cycle has elapsed since the last subject's first dose in the previous cohort. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level (**Table 5**). If only 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more subjects within a cohort experience DLTs, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced. Approximately 50 subjects will be enrolled into the dose escalation phase of the study.

Table 4: Part 1: Sample Dose Escalation Scheme

Cohort	NKTR -214 Dose
Cohort 1	0.003 mg/kg
Cohort 2	0.006 mg/kg
Cohort 3	0.012 mg/kg
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The Sponsor and at least one Investigator will jointly decide the following:

- Dose levels for a given cohort, as listed in **Table 4**, may be reduced by 25-50% depending on the severity, duration, and frequency of toxicities observed at the previous dose level as well as the PK profile, if available.
- In the event that MTD is not determined at the highest dose level listed in the table, dose escalation at no more than 100% higher than previous dose may continue.
- The schedule of dosing can be modified to every 14 or 28 days based on a review of the safety data and available PK data.
  - Note, the first dose level for every 14-day cohort will be determined as follows: If MTD has been reached in the 21-day dosing cohort, the dosing level will be at least one dose lower than MTD. If MTD has not been reached in the 21-day dosing cohort, the dosing level will be at least one dose lower than the highest dosing cohort tested in the 21-day dosing cohort.
  - The first dose level for every 28-day cohort will be either the MTD using the 21-day dosing cohort (if determined) or the highest dosing cohort tested in the 21-day dosing cohort (if MTD not determined).
- Once the MAD has been reached, lower doses and different dose schedules may be assessed, within the anticipated total number of subjects of approximately 50.

Table 5: Dose Escalation Rules

Number of Subjects with DLT at a Given Dose Level	Dose Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next higher dose level.
1 out of 3	Will enter at least 3 more subjects at this dose level. If 0 of these additional 3 subjects experience a DLT, will proceed to the next dose level. If 1 or more of this group suffers a DLT, then the dose escalation is stopped, and this dose is declared the MAD. Three (3) additional subjects will be entered at a lower dose level if only 3 subjects were treated previously at that dose.
≥ 2	Dose escalation will be stopped. This dose level will be declared the MAD (highest dose administered). Three (3) additional subjects will be entered at a lower dose level if only 3 subjects were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is the MTD. At least 6 subjects must be entered at the recommended dose for the phase 2 recommended dose.

4.1.2.2 Part 2: Dose Expansion Scheme

At least 1 study Investigator and the Sponsor Medical Monitor will meet and decide the dose to be studied in Part 2 before the initiation of the dose expansion cohort (either the MTD dose or dose lower than MTD). This dose will be the recommended Phase 2 dose (RP2D), and all subjects in the expansion cohort will receive this dose. The RP2D may also be determined based on a biological effect of the study drug as determined by anti-tumor activity and immune activation. The RP2D for dose expansion will be communicated via an administrative dosing letter and enrollment in the expansion phase may begin without a protocol amendment.

Approximately 50 subjects with renal cell carcinoma (RCC) will be enrolled into Part 2. Subjects in the expansion cohort will be treated until tumor progression (treatment may continue if there is clinical benefit), death, unacceptable toxicity, symptomatic deterioration, achievement of maximal response, subject choice, the Investigator's decision to discontinue treatment, the subject withdraws consent, or Nektar Therapeutics decides to terminate the trial.

Note: The sponsor reserves the right to evaluate two doses or two dosing schedules in each expansion cohort if necessary based on the safety profile during the dose escalation portion.

4.1.3 Tumor Assessments

Tumor response assessments for all subjects will occur every 8 weeks (± 7 days) (see Section **9.0**). Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Subjects with progressive disease (PD) but with otherwise stable or improved performance and clinical status may continue to be treated with study drug in the event of a perceived benefit per Investigator (e.g., non-availability of alternate standard of care therapies). Subjects with a partial response (PR) or stable disease (SD) will continue to receive NKTR-214 until achievement of a confirmed complete response (CR), disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating subjects with a confirmed CR.

4.1.4 Post-treatment

Subjects who discontinue NKTR-214 due to reasons other than radiographic disease progression will continue radiologic tumor assessments every 3 months until disease progression per RECIST v1.1 or start of subsequent anti-cancer therapy. Subjects will also be contacted for survival every 3 months until death, withdrawal of consent, study termination by the Sponsor, lost to follow-up, or for a maximum of 3 years after Cycle 1 Day 1.

A schematic of the study design is presented in Section **1.1** and the Schedule of Assessments for the Dose Escalation and Dose Expansion cohorts is in Section **1.2**.

5.0 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

For Parts 1 and 2

1. Willing and able to provide written informed consent.
2. Histologically confirmed diagnosis of a locally advanced (not amenable to curative therapy such as surgical resection) or metastatic solid tumor.
3. Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF)
4. Life expectancy >12 weeks.
5. Patients must not have received interleukin-2 [IL-2] therapy within 12 months of Cycle 1 Day 1.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
7. Measurable disease per RECIST v1.1
8. Sample of archival tumor tissue and fresh baseline tumor biopsies (fresh baseline biopsy is defined as a biopsy specimen taken within 28 days prior to Cycle 1, Day 1) are required, except if inaccessible with Medical Monitor approval. Subjects must consent to allow acquisition of existing formalin-fixed paraffin-embedded (FFPE) material, either a block or unstained slides for performance of correlative studies.
9. Demonstrated adequate organ function, as defined below, within 14 days of treatment initiation:
    a. WBC count $\geq$ 2000/μL (after at least 7 days without growth factor support or transfusion)
    b. Absolute neutrophil count (ANC) $\geq$ 1500/μL (after at least 7 days without growth factor support or transfusion)
    c. Platelet count $\geq$ 100x 10^3/μL (transfusions allowed)
    d. Hemoglobin $\geq$ 9.0 g/dL (transfusions allowed)
    e. Serum creatinine $\leq$ 2 mg/dL (or glomerular filtration rate $\geq$ 40 mL/min)

f. Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3X upper limit of normal (ULN)

g. Total bilirubin within normal limits unless associated with hepatobiliary metastases or Gilbert's syndrome, in that case total bilirubin ≤ 2x ULN

10. On stress echocardiogram, documented left ventricular ejection fraction >45% on cardiac stress test within 60 days prior to Cycle 1 Day 1. At the discretion of the Investigator, patients who are unable to perform a stress echocardiogram may instead have a multigated acquisition (MUGA) scan or transthoracic echocardiogram (TTE).

11. Oxygen saturation ≥ 92% on room air. NSCLC patients may use supplemental oxygen.

12. Clinically significant toxic effect(s) of the most recent prior chemotherapy must be resolved to Grade 1 or less (except alopecia and sensory neuropathy). Immune-related AEs from previous therapy must be resolved to Grade 0 (except for endocrinopathies, or rash, which can be Grade 1). If the subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

13. Women of childbearing potential must agree to use highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate [i.e., < 1% per year] when used consistently and correctly, such as oral contraceptives, surgical sterilization, an intrauterine device, and/or 2-barrier methods [e.g., condom and cervical barrier such as a diaphragm]). Protections against pregnancy must be continued for at least 3 months after the last dose of study drug. All subjects must agree to use double-barrier contraception during participation in this study and for at least 3 months after the last dose of study drug. This criterion may be waived for male subjects who have had a vasectomy > 6 months before signing ICF.

[redacted]

e. Clinically asymptomatic in screening.

15. **For expansion cohort only:**

Renal Cell Carcinoma (RCC)

a. Histologically confirmed diagnosis of unresectable or metastatic RCC with predominantly clear cell elements

b. Must have received only 1 prior line of anti-angiogenic therapy.

c. Must not have received prior immunotherapy with immune-modulators including but not limited to checkpoint inhibitors such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody and any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways, indoleamine 2,3-dioxygenase pathway inhibitors, cancer vaccines, adoptive cell therapies, and cytokine therapies.

5.2 Exclusion Criteria

1. Use of an investigational agent or an investigational device within 28 days before administration of first dose of NKTR-214.

2. Females who are pregnant or breastfeeding.

3. Subjects who have an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents. (Exceptions include any subject on 10 mg or less of prednisone or equivalent, subjects with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema, or with Medical Monitor approval.)

4. History of organ transplant that requires use of immune suppressive agents.

5. Use of warfarin within 14 days of initiating NKTR-214. (Note: Low molecular weight heparin is allowed on the study).

6. Evidence of clinically significant interstitial lung disease or active, noninfectious pneumonitis.

7. Active central nervous system (CNS) metastases.

8. Prior surgery or radiotherapy within 14 days of therapy. Subjects must have recovered from all radiation-related toxicities, not required corticosteroids and have not had radiation pneumonitis.

9. Subjects who have had < 28 days since the last chemotherapy, immunotherapy, biological therapy, or < 14 days from approved tyrosine kinase inhibitor (TKI) therapy (sunitinib, sorafenib, vemurafenib, dabrafenib, cobimetinib), or systemic or inhaled steroid therapy at doses greater than 10mg of prednisone or equivalent before administration of the first dose of study medication.

10. Active infection requiring systemic therapy.

11. Has known hepatitis B virus (HBV) infection (e.g. HBsAg reactive) or hepatitis C virus (HCV) e.g., HCV RNA qualitative is detected).

12. Has known immunodeficiency or active human immunodeficiency virus (HIV 1/2 antibodies).

13. Prolonged QTcF >450 milliseconds (ms) for men and >470 ms for women at Screening

14. History of unstable or deteriorating cardiac disease within the previous 6 months prior to screening including but not limited to the following:

    a. Unstable angina or myocardial infarction

    b. Congestive heart failure (New York Heart Association [NYHA] Class III or IV)

    c. Uncontrolled clinically significant arrhythmias

15. Need for > 2 antihypertensive medications for management of hypertension.

16. Known current drug or alcohol abuse.

17. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the subject from adhering to the protocol.

5.3 Removal of Subjects from Study Therapy or Assessment

Subjects may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment.

Subjects may stop participating in or be withdrawn from the study for any of the following reasons, but are to be followed according to the procedures section for progression of disease and for safety until resolution or permanent sequelae of all toxicities attributable to the study drug.

- Subject has progressive disease,
- Occurrence of a clinically significant AE found to be unacceptable by the Investigator;
- Subjects who need more than 6 weeks to recover from treatment-related toxicities;
- Symptomatic deterioration,
- Achievement of maximal response,
- Noncompliance of the subject with protocol-mandated procedures based on agreement of both the Investigator and Sponsor;
- Continued participation is no longer in the subject's best interest in the opinion of the Investigator;
- If a female subject becomes pregnant, administration of the study drug must be discontinued immediately;
- Withdrawal of Consent;
- The study is terminated by the Sponsor.

In the event of a subject's withdrawal, the Investigator will promptly notify the Sponsor and make every effort to complete the Early Termination assessments specified in the Schedule of Assessments (Section **1.2**).

6.0 TREATMENT PLAN (DOSE ESCALATION AND DOSE EXPANSION)

6.1 Overview

The study has a screening period, treatment period and post-treatment period. All procedures are outlined in the Schedule of Assessments (Section **1.2**).

6.2 Screening Period

Subjects will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to part of the subject's normal care. After signing the ICF subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug.

6.3 Treatment Period

Subjects who meet the selection criteria may start NKTR-214 treatment within 28 days following the Screening visit. The treatment period of the study is divided into multiple 21-day cycles with associated evaluations and procedures. Results of the assessments must be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted escalation of dose level after assignment to a specific NKTR-214 dose level. Dose reductions after Cycle 1 due to AEs may occur following a discussion with the site Investigator and Medical Monitor. Every effort should be made to schedule visits within the protocol-specified windows.

For each dose level in Part 1, the first subject enrolled into a given dose cohort will be treated and monitored from Cycle 1, Day 1 through Cycle 1, Day 5 for safety and tolerability prior to dosing of additional subjects at that dose level.

Cycle 1, Day 1 will be the first day of treatment with NKTR-214 and Cycle 2, Day 1 will be the first day of the second dose of NKTR-214. Results from Day 1 laboratory evaluations must meet eligibility criteria prior to Cycle 1, Day 1 dosing.

During dose escalation, subjects who drop out prior to completion of Cycle 1 will be replaced unless the subject discontinued due to a DLT. During dose expansion, subjects will not be replaced.

Subjects will be treated until unacceptable toxicity, or disease progression per RECIST version 1.1. In the presence of disease progression, treatment may continue if there is clinical benefit as determined by the Investigator based on a reduction of symptoms related to cancer and absence of clinical deterioration or decline in ECOG performance status.

Note: Dosing may change to q14d or q28d following review and agreement by the Sponsor and Investigators. The change in cycle length will be determined by review of safety data and PK review of study drug.

After completing the pre-dosing procedures, administer NKTR-214 as an IV infusion over 15 ± 5 minutes (Section **6.11**).

Postdosing:

- The study site must be equipped for medical emergencies and have access to an intensive care unit.
- During dosing days, subject will stay in clinic for observation approximately 1 hour after dosing.
- Administer at least 2 liters of fluid (IV or self-administered orally [e.g., fluid containing electrolytes]) during Days 1 to 5 of every cycle.
- Advise subjects to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 5 of every cycle (Parts 1 and 2, dose escalation and expansion).
- Should a subject experience hypotension at any time during a cycle, IV fluid administration has been effective. Subjects with adrenal insufficiency requiring corticosteroid supplementation may benefit from additional short term corticosteroid use of up to 5mg/day of prednisone for the management of hypotension. Vasopressors may also be used for hypotension.
- A Patient Wallet Card is available that contains important safety information.

Vital Signs

Vital signs (temperature, pulse, respiration, systolic and diastolic blood pressure, and oxygen saturation), concomitant medications, and potential AEs will be assessed either at the study site or as a Home Health visit as needed. Qualified home health personnel may visit the subject to take vital sign measurements. The results of these measurements will be provided to the Investigator or designee. The Investigator will be responsible for assessing any adverse events and for following up with the subject.

6.4 Radiographic Assessments

Radiographic assessments (chest/abdomen/pelvis) by computed tomography (CT) scan or magnetic resonance imaging (MRI) are required for all subjects for tumor measurements. CT

scans or MRIs will be performed, target lesions measured, and tumor response evaluation completed at Screening (within 28 days prior to Cycle 1 Day 1) and every 8 weeks (± 7 days) from Cycle 1 Day 1 while on study treatment, until PD is noted (even if subject has stopped treatment with study drug) or the subject withdraws consent.

The same method of assessment (CT or MRI) and the same technique for acquisition of images must be used for all study assessments. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study. Radiographic assessments will also be conducted by an independent central imaging core laboratory for all dose escalation and dose expansion cohorts. There must at least one measurable solid tumor by RECIST version 1.1 present on the Screening scan.

6.5 Post-treatment Period

The EOT/Early Termination visit is to occur within 30 days (+ 10 days) after last dose of study drug.

Subjects who reach the EOT visit without radiographic disease progression must continue to undergo immunogenicity testing and radiological assessment at the interval of every 3 months (±7 days) until either disease progression per RECIST version 1.1 or the start of a new anti-cancer therapy. Subjects will also be followed every 3 months (±7 days) for survival until death, lost to follow-up, study termination by Sponsor, or 3 years have passed since the subject's first dose.

For any toxicity the Investigator attributed to study drug, the Investigator will assess the subject to determine whether the toxicity resolved or worsened. Information on whether the toxicity resolved or worsened must be entered into the eCRF.

6.6 Pharmacokinetic Measurements

Blood samples for pharmacokinetic analysis will be collected and processed as outlined in a Laboratory Manual that will be provided to the site. Briefly, at each designated sampling time, using Sponsor-provided kits, collect 2 mL or 4 mL whole blood into tubes; centrifuge to obtain plasma. Aliquot plasma in plasma storage tubes, freeze, and ship as outlined in the Laboratory Manual.

For all PK blood samples, the date and actual time collected must be recorded. For subjects whose only peripheral access is via a venous access device or peripherally inserted central catheter, refer to the Laboratory Manual for the proper technique to ensure undiluted whole blood for PK assessments.

6.7 Immunogenicity Measurements

Serum samples will be collected and processed as outlined in the Laboratory Manual that will be provided to the site. Briefly, at each designated time point, collect 5-10 mL of blood into serum collection tube, harvest serum, freeze, and ship as outlined in the Laboratory Manual.

6.8 Biomarker Measurements

Blood and tumor tissue biopsies will be collected and processed as outlined in the Laboratory Manual that will be provided to the site. Briefly, for blood biopsies, at each designated time point, collect 4x10 mL of blood into green-topped blood collection tubes and 1x10 mL of blood into red-topped blood collection tubes. For optional blood biopsies at time of optional tumor biopsies, collect 1x10 mL of blood into green-topped blood collection tube. For tumor biopsies, collect core biopsies or biopsies with a volume ≥ 100 mm^3, and divide into 3 portions. One portion will be FFPE for immunohistochemistry (IHC) analysis, one portion will be used for RNA isolation and molecular characterization, and one portion will be used to analyze TILs using flow cytometry. Refer to the Laboratory Manual for specific instructions on sample processing, storage, and shipping.

6.8.1 Biomarker Blood Collection Times and Assessments

Blood for biomarker analysis will be collected as described in the Schedule of Assessments (Section **1.2**). The whole blood correlative pharmacodynamic samples will be analyzed by flow cytometry for changes in markers of immune cell populations, including, but not limited to, markers for immune cell populations (T lymphocytes, B lymphocytes, natural killer cells, monocytes, memory T cell subsets, Tregs, and T-cell activation). In addition, whole blood samples will be obtained for evaluation in assays of immune function such as stimulated cell activation (assessed by marker expression, cytokine secretion, proliferation, etc.), isolation of peripheral blood mononuclear cells to assess immunodiversity, and miRNA/mRNA analysis, and genetic profiling.

6.8.2 Tumor Tissue Biopsy Collection Times and Assessments

Archival tumor samples and fresh tumor biopsies (defined as a biopsy specimen taken within 28 days prior to the first dose of study treatment) will be required at baseline. For archival unstained tumor samples, a minimum of 10 slides must be submitted (no more than 30 days after first dose). Exceptions may be made with Medical Monitor approval in cases where fresh tumor tissue and/or archival tumor samples are inaccessible. A biopsy specimen from a sample taken since completion of the most recent prior systemic treatment may be acceptable in lieu of a fresh biopsy with medical monitor approval. Tumor biopsy collection is described in the Schedule of Assessments (Section **1.2**). Exceptions will be made with Medical Monitor approval in cases

where tumor tissue is inaccessible. Only 20 tumor biopsies will be collected in Part 2. Biopsies should be performed on lesions that have not been exposed to prior radiation. Tumor lesions used for biopsy should not be lesions used as target lesions, unless there are no other lesions suitable for biopsy. If a target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter. Pre- and post-treatment tumor tissue biopsies should be taken from the same lesion, if feasible. Tumor tissue biopsies will be used for characterization of infiltrating immune cell populations using a panel of markers (including, but not limited to CD3, CD4, CD8, CD25, FoxP3, CD68, CD56, CD20, CD45RO, PD-1, CTLA-4, and granzyme B), using IHC, flow cytometry, mass spectroscopy, or other similar techniques. Biopsy samples may also be used to investigate molecular signatures. DNA and/or RNA may be extracted from these samples to do somatic mutation analysis and gene expression analysis. Genes to be assayed may include, but not be limited by those with known driver mutations in solid tumors. These samples will be analyzed by the sponsor or designee.

6.8.3 Stool Sample Collection Times and Assessments

A stool sample from a single bowel movement will be collected by subjects participating in the expansion phase of the study prior to administration of the first dose. Subjects will be provided with a materials kit and instructions for collecting the stool sample. Stool samples will be processed to extract and sequence microbial DNA and RNA as outlined in a Laboratory Manual.

6.9 Determination of Dose-Limiting Toxicities

Based on the preclinical toxicology data and the anticipated half-life of NKTR-214 (15-20 hours), drug-related toxicity is most likely to occur during treatment or within 10 days following treatment. Based on this, dose-limiting toxicities (DLTs) will be assessed in the first cycle for all subjects enrolled to a specific cohort (same dose level). If DLTs are not observed, dose escalation will be permitted and enrollment will begin at the next successive ascending dose cohort. Intra-subject dose escalation will not be permitted. Dose reduction is allowed in subjects based on toxicity with approval from the Medical Monitor.

Unless otherwise suggested by clinical data, a dose-limiting toxicity (DLT) is defined as a Grade 3 or higher study drug-related or possibly related AE occurring within the first cycle of dosing (excluding Grade 3/4 transient lymphopenia < 14 days in duration, tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor, a transient, reversible ≤ grade 3 infusion AE, non-clinically significant laboratory abnormalities, or fatigue lasting less than 72 hours) using NCI CTCAE version 4.03.

Delayed DLTs are drug-related adverse events that occur after Cycle 1. Delayed DLTs will not be used to determine the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and the Sponsor on an ongoing basis.

All drug related adverse events after Cycle 1 will continue to be collected and evaluated by the Investigators and the Sponsor on an ongoing basis and will be taken into consideration in determining the MTD.

All AEs that meet DLT criteria**,** as well as any ≥ Grade 3 immune-related adverse event (regardless of attribution), must be reported to the Sponsor, within 24 hours using the same rapid notification procedures that are used for serious AEs (Section **8.7**).

6.10 Dose Modifications

6.10.1 Non-immune-related Adverse Events

- Grade 1 or 2 toxicity: No requirement for dose delay or dose reduction. If the toxicity persists at Grade 2 following completion of Cycle 1, a dose reduction to the next lower NKTR-214 dose level (for dose escalation) or 50% of the assigned dose (dose escalation or dose expansion) may be implemented at the discretion of the Investigator with the approval of the Medical Monitor.

- Grade 3 toxicity: NKTR-214 may be withheld if toxicity cannot be managed by adequate medical intervention. NKTR-214 dosing may resume at the same dose or the next lower NKTR-214 dose level (for dose escalation) or 50% of the assigned dose (dose escalation or dose expansion) when toxicity resolves to Grade 1 or returns to baseline, except for instances consistent with clinically significant capillary leak syndrome or where the potential recurrence of the event poses an undue risk for the subject.

- Grade 4 toxicity (excluding Grade 4 transient lymphopenia < 14 days in duration): Dosing should be permanently discontinued.

6.10.2 Immune-related Adverse Events

Permanently discontinue NKTR-214 for:

- Grade 2 or 3 immune-related AEs (irAEs) that do not improve to Grade 0 or 1, except endocrinopathies managed with replacement hormones

- Grade 3 irAEs that recur at ≥ Grade 3

- Grade 3 immune-related pneumonitis, colitis, hepatitis, pancreatitis

- Grade 4 irAEs, except endocrinopathies managed with replacement hormones
- Any uveitis event

Subjects who need more than 6 weeks to recover from treatment-related toxicities should be removed from study treatment.

6.11 Administration of NKTR-214

The subject's weight in kilograms will be determined before the start of each cycle. Each subject's NKTR-214 dose will be determined by the dose escalation scheme and the subject's weight in kilograms. NKTR-214 will be administered as an intravenous (IV) infusion over 15 ± 5 minutes.

Pre-medications should not be administered prior to the initial administration of NKTR-214, but if a subject reports symptoms (such as nausea and/or vomiting), prophylactic use of anti-emetics may be used.

The administration of NKTR-214 will be captured in the source documents and recorded on the electronic case report form (eCRF). The lot number for the NKTR-214 vials will be captured on Drug Accountability Log.

Refer to the Pharmacy Binder for further information.

6.12 Infusion Delays and Missed Doses

In exceptional circumstances, NKTR-214 administration may be delayed. NKTR-214 administrations that cannot be done within 7 days will be considered a missed dose, and the subject should come in for their next, regularly scheduled visit. The next scheduled visit should occur according to the subject's next regularly scheduled visit relative to Day 1. The Medical Monitor should be notified if a subject misses 3 consecutive doses. If a subject misses multiple consecutive doses of study drug, the subject may be considered discontinued with Medical Monitor approval.

6.13 Prior and Concomitant Medications

All medications (prescription and over-the-counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the subject from Screening through the EOT visit will be documented, and recorded on the concomitant medication eCRF and will include start and stop date, dose and route of administration, frequency and indication. Medications taken for a procedure (e.g., biopsy) should also be included.

6.14 Permitted Medications

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care (including flu vaccines). All concomitant medications administered to study subjects will be captured in source documents and recorded on the eCRF.

6.15 Prohibited Medications

Any anti-cancer therapy (other than NKTR-214), investigational agent, or radiation therapy is prohibited during the study. Palliative radiation is permitted to 1 non-target lesion at a time, provided it is completed 14 days before dosing of NKTR-214. Subjects with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with NKTR-214. For these subjects, their existing corticosteroid dose may be increased by an additional supplementation of up to 5 mg/day of prednisone, or equivalent, for the first 4 days after administration of NKTR-214 based on an assessment of the degree of adrenal impairment and the extent of existing corticosteroid supplementation.

Consideration should be given to discontinuing antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (e.g., alpha blockers for BPH), prior to each dose of NKTR-214, particularly when therapy involves multiple antihypertensive drugs and classes other than thiazide diuretics. Antihypertensive medications should be discontinued no less than 12 hours and no more than 48 hours prior to each dose of NKTR-214. Antihypertensive medications may be reinstituted in between doses of NKTR-214 if the diastolic pressure exceeds 90 mmHg and/or the systolic pressure exceeds 160 mmHg.

6.16 Adverse Events

All AEs, either reported by the subject or observed by study staff, will be recorded in the source documents and in the eCRF. This trial will use the Medical Dictionary for Regulatory Activities (MedDRA 18.1 or later) for coding all AEs. AEs within each system will be summarized by preferred term, system organ class, NCI-CTCAE version 4.03 grade of severity, and relationship to the study drug.

6.17 Assigning Subject Numbers

Each subject will be assigned a unique subject number after signing the ICF. This subject number will be used on all subjects' study information. Subject numbers will not be reassigned.

7.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

7.1 Description and Formulation

The investigational drug product, NKTR-214, is formulated as a sterile lyophilized powder for reconstitution in single-use glass vials. Lyophilized NKTR-214 drug product will be diluted with commercially available Dextrose 5% in water for injection (D5W). Each 5 mL, clear glass, single-use vial contains 1.1 mg of recombinant human interleukin 2 (rhIL-2) equivalence (including 0.1 mg of overage). NKTR-214 is formulated in 10 mM citrate buffer, 7% (w/v) trehalose, pH 4.0.

7.2 Study Drug Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (cGMP). The lyophilized drug product is packaged in a Schott 5 mL, 13 mm opening, USP Type I glass serum lyophilization vial with 13 mm Westar® coated gray rubber stoppers and aluminum crimps with flip cap. Secondary packaging will be cardboard box with foam inserts holding up to 10 vials.

Each vial will be labeled with the study drug number/name, strength, name of the Sponsor, storage condition, lot number and the required cautionary statement.

7.3 Study Drug Reconstitution and Handling

The instructions for reconstitution and administration of NKTR-214 drug product are described in the Pharmacy Manual.

7.4 Study Drug Storage

NKTR-214 drug product should be stored in a secure, locked area with temperature at -20°C (± 5°C), as specified on the drug label.

7.5 NKTR-214 Drug Shipment

Supply of NKTR-214 drug product will be shipped frozen (-20°C) to the site pharmacy upon completion of the site activation process.

Please refer to the Pharmacy Manual for additional details for ordering drug supply.

7.6 Study Drug Accountability and Reconciliation

All study drug will be supplied to the Investigator by Nektar Therapeutics or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Nektar Therapeutics at the end of the study.

The Drug Accountability Log may record specifics to study drug dispensation such as:

- Records of product delivery, inventory, temperature monitoring, destruction, and return as per Sponsor's instructions
- Dosages prepared, time prepared, doses dispensed
- Doses and/or vials destroyed

The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

8.0 ASSESSMENT OF SAFETY OR AES AND SERIOUS AES

8.1 AE Definition and Assessment

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, at any dose, not necessarily related to the treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of administration, formulation, dose, or overdose. This definition includes intercurrent illnesses or injuries, and exacerbation of preexisting conditions. Clinical laboratory abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator and/or are associated with signs and symptoms, require treatment, or require follow-up.

An AE does not include:

- A medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure
- Pre-existing diseases or conditions present or detected before start of study medication administration which do not worsen or increase in severity or frequency after the administration of study medication
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a subject)
- Overdose of either study medication or concomitant medication without any signs or symptoms

8.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded on the appropriate eCRF including but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug, outcome, treatment of the event, and action taken with the study drug. AEs will be reported starting immediately after the subject has been administered the first dose of study medication through 30 days after the last dose of NKTR-214.

An event occurring after the subject has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator OR there is a significant change in the rate

of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Under the latter two circumstances, the event will be considered an AE and will be captured as such on the eCRF.

Example 1:

Thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is an event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be captured as an AE on the eCRF page, and it will be documented as being "unrelated" to study drug as applicable.

Example 2:

An ankle sprain following an unexpected fall from a flight of stairs while at home, after the subject has provided informed consent, but before the first dose of study drug, is clearly unrelated to any protocol-mandated procedures and would therefore be captured as medical history in the medical history section of the eCRF.

8.3 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of event is based on the subject/event outcome or action criteria. All AEs will be assessed for severity using the NCI-CTCAE version 4.03. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

- Grade 1 = Mild (event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache)
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication)
- Grade 3 = Severe (event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention).
- Grade 4 = Life threatening or disabling
- Grade 5 = Death

AEs will be reported with an individual start and stop date for each level of severity.

8.4 Causality Relationship of AEs

The relationship of each AE to the study treatment (NKTR-214) as applicable will be evaluated by the Investigator using the following definitions:

- Not related: The AE is clearly not related to the investigational agent(s). The AE can be explained to be likely related to other factors such as concomitant medications or the subject's clinical state.

- Possibly related: The AE may be related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE and it follows a known response pattern to the investigational product. The reaction may have been produced by the subject's clinical state or other concomitant therapies or interventions.

- Related: The AE is clearly related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE and it follows a known response pattern to the investigational product. The occurrence of this AE can be confirmed with a positive re-challenge test or supporting laboratory data.

The causality criteria of related and possibly related will be considered "related" to the study medication for regulatory reporting requirements.

8.5 AE Reporting and Follow-up

Adverse events will be reported from the time of first study drug administration until 30 days after the last dose of study drug. All ongoing AEs will be followed until resolution, the subject is lost to follow-up, subject death, or until 30 days after last dose of study treatment, whichever is earlier. In case the AE has not completely resolved up to 30 days after last dose of study treatment, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable. Any new AEs occurring more than 30 days after last dose of study treatment will not be captured unless related to study drug.

For specific instructions on identifying and reporting SAEs, see Sections **8.6** and **8.7**.

8.6 Serious AE Definition

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening, i.e., in the opinion of the Investigator, the AE places the subject at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient- hospitalization or prolongation of an existing hospitalization that occurs during the course of a subject's participation in a clinical study, except for those due to the following:
  - A surgery or procedure that was planned before the subject entered the study and which is part of the planned study procedure.
  - Nonmedical reasons, in the absence of an AE.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above

Death is an outcome of an AE, and not an AE in itself. All deaths regardless of causality must be reported. An efficacy failure is not considered an SAE. "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity. "Inpatient hospitalization" means the subject has been admitted to a hospital for medical reasons for any length of time. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

8.7 Serious AE Reporting

SAEs with an onset within 30 days after the subject's last dose of study treatment, but before initiation of a new antineoplastic treatment, will be reported to Nektar Therapeutics Drug Safety within 24 hours of when the site becomes aware of the event. It is anticipated that some patients will experience disease progression before study discontinuation, and the disease progression may result in hospitalization or death. Adverse events leading to hospitalization or death typically are considered serious and require reporting on a serious adverse event form. In addition, disease progression per se is already captured as an efficacy endpoint. Where possible,

the specific event defining the disease progression should be reported, such as pleural effusion, intestinal obstruction or cardiac failure. Only if it is not possible to discern the specific event leading to disease progression, should "disease progression" be reported as the event. In addition, SAEs that are assessed by the Investigator as possibly or related to study medication and occurring **> 30 days** after last dose of study treatment will also be reported to Nektar Therapeutics Drug Safety within **24 hours** or when the site becomes aware of the event.

[redacted]

The Investigator must complete the SAE Report Form, assess the causality relationship to the study treatment as applicable, and send the completed SAE form via email or fax to Nektar Therapeutics Drug Safety. A follow-up report and any additional records (such as hospital records, consultant reports, and autopsy findings) will be emailed or faxed to Nektar Therapeutics Drug Safety within **24 hours** of receipt. Any medication or other therapeutic measures used to treat the event will be recorded.

All SAEs will be followed as described in Section **8.8**.

Reporting of SAEs to the Institutional Review Board (IRB) will be done in accordance with the standard operating procedures (SOPs) and policies of the IRB. Adequate documentation must be provided to Nektar Therapeutics, showing that the IRB was properly notified. Serious AEs will be reported by Nektar Therapeutics or designee to the Regulatory Authorities, per local regulations.

8.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved within 30 days of last dose of study treatment as applicable, will be followed until any of the following occur (whichever comes first):

- The event resolves
- The event has stabilized
- The event returns to baseline, if a baseline value is available

- It is unlikely that any additional information can be obtained (e.g., subject or health care practitioner refuses to provide additional information; lost to follow-up after demonstration of due diligence with follow-up efforts)

- The subject dies or is lost to follow-up.

All ongoing SAEs assessed as "unrelated" to study medication will be followed until resolution or until 30 days after last dose of study medication, whichever is earlier. In the case where an unrelated SAE has not completely resolved up to 30 days after last dose of study treatment, the final outcome of these ongoing SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

8.9 Immune-Related Adverse Event Reporting

Immune-related adverse events (irAE) are considered adverse events of special interest due to their potential clinical significance. Investigators should use clinical judgment to determine that an adverse event is immune related, and are encouraged to rule out neoplastic, infectious, metabolic, toxic or other etiologies, to the extent possible, before characterizing an event as immune related.

Grade 3 or higher immune-related adverse events, with an onset within **30 days** after the subject's last dose of study treatment, must be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event.

[redacted]

The Investigator must complete the SAE Form, mark the report as an immune related adverse event and send the completed form via email or fax to Nektar Therapeutics Drug Safety. Any medication or other therapeutic measures used to treat the event will be recorded. A follow-up report will be emailed or faxed to Nektar Therapeutics Drug Safety as soon as additional details become available.

8.10 Pregnancy

The sponsor must be notified within 24 hours of the initial report and any follow-up reports of a male subject's female partner or a female subject becoming pregnant during the course of the

study and for 3 months after the last dose of the study drug. Pregnancy, although reportable, is not considered an AE/SAE unless a female subject or male subject's female partner experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section **8.7**. Females who become pregnant will be followed every trimester until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

If a female subject becomes pregnant, administration of the study drug must be discontinued immediately.

8.11 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Assessments (Section **1.2**). Clinical laboratory tests will be performed by the local laboratory for the Dose Escalation phase and central laboratory for the Dose Expansion phase. Clinical laboratory test data will be reviewed by the Investigator or qualified Sub-investigator. Additional clinical laboratory tests may be ordered at the Investigator's or qualified Sub-investigator's discretion. Additional testing for PK and biomarkers will be performed by the designated central laboratory.

The Investigator or qualified Sub-investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (i.e., are associated with signs and symptoms, require treatment or require follow-up) will be recorded as an AE as described in Section **8.1**.

8.12 Vital Signs

Vital sign measurement will be recorded at every visit. Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature (oral).

8.13 Electrocardiograms

Five-minute summary ECGs will be performed on a calibrated 12-lead machine according to the Schedule of Assessments (Section **1.2**). Subjects must be resting quietly in the supine position for at least 5 minutes before the ECG. ECG recordings will start at 5 minutes before the time point and end at the time point. All ECGs should be recorded before any corresponding PK samples are obtained. Interpretation of ECGs and interval duration measurements will be performed by a designated ECG laboratory. Interpretation of ECGs and interval duration measurements will be provided to the site.

At each time point, 5 minutes of ECG data will be recorded. The 5 minutes of ECG data is converted into a Summary ECG (simulated 10-second ECG) for each subject. The Summary ECG is then submitted to CalECG (version 3.3.0) and the Glasgow algorithm (version 27.0.2) for measurements and diagnoses, and to the Cardiologist over-reader for confirmation, as though it were a standard 10-second ECG.

The Investigator or qualified Sub-investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE as described in Section **8.1**. Subjects who are discontinued will be required to complete the ET visit and all safety follow-up procedures.

8.14 Pregnancy Tests

Serum pregnancy tests will be performed on women of childbearing potential during screening. Urine or serum pregnancy tests will be performed on women on Day 1 of each cycle prior to dosing. A negative pregnancy test result must be obtained before the administration of the study drug.

A pregnancy test does not need to be performed on women who are postmenopausal for at least 1 year or surgically sterile for at least 3 months before signing the ICF.

If a female subject becomes pregnant, administration of the study drug must be discontinued immediately.

9.0 ASSESSMENT OF EFFICACY EVALUATIONS

Documented tumor measurements are required using CT scans or MRI, as appropriate and are to be performed every 8 weeks (± 7 days) and in line with standard of care. The same method of assessment (CT or MRI) and the same technique for acquisition of data must be used to characterize each identified and reported lesion at baseline, during the treatment period, and at the EOT visit (if previous assessment was not completed within 4 weeks).

Radiological imaging must include the pelvis, abdomen, and chest.

All subjects must have tumor measurements performed at the participating study center.

Efficacy analyses will be on data provided by the investigator site as well as an independent central imaging core laboratory. Site training, data collection, and analysis of all scans acquired during the study as per schedule of assessments will be detailed in a study manual and imaging charter.

Response and progression will be determined using the RECIST guidelines (version 1.1) (**Eisenhauer, 2009**)

9.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

9.1.1 Measurable Disease

Target tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm); when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.1.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions, are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

9.2 Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. For cutaneous lesions that are included in target lesions, digital photographs should be obtained and utilized for measurement.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. If a slice thickness > 5 mm is used for CT scanning, then the minimum longest diameter for a target lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the ULN, however, they must normalize for a subject to be considered in complete response.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases when the nature of a residual lesion is in question. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

9.2.1 Tumor Response Evaluation

9.2.1.1 Assessment of Overall Tumor Burden at Baseline and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

9.2.1.2 Baseline Documentation of 'Target' and 'Non-target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of 2 and 4 lesions, respectively, will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

9.2.1.3 Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination),

even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, if the lesion is believed to be present and is faintly seen but too small to measure with any accuracy, a default value of 5 mm should be assigned.

9.2.2 Response Criteria using RECIST v1.1

9.2.2.1 Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline SLD
Progressive Disease (PD)	At least a 20% increase in the SLD of target lesions, taking as reference the smallest SLD on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is considered progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

9.2.2.2 Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points of radiographic assessments.

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

NOTE: If tumor markers are assessed for a given subject and are initially above the ULN, they must normalize for a subject to be considered in complete CR.

9.2.2.3 Confirmatory Measurement/Duration of Response

9.2.2.3.1 Confirmation

Confirmation of response (either PR or CR) is required. Changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 4 weeks after the criteria for response are first met.

9.2.2.3.2 Duration of Overall Response

DOR is measured from the time that measurement criteria are met for CR or PR (whichever is first recorded) until a documented PD per RECIST 1.1 or death.

9.2.2.4 Evaluation of Overall Response using RECIST v1.1

Table 6: Best Overall Response When Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise. PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise. PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise. NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise. PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise. NE
NE	NE	NE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

a. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Source: **Eisenhauer, 2009**

10.0 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

10.1 General Considerations

All analyses will be descriptive in nature and subject data will be listed. Descriptive statistics will be presented by dose level and for all subjects, and further summarized by tumor type.

All subjects that received at least 1 dose (or partial dose) of NKTR-214 will be considered evaluable for safety analysis. Safety will be assessed by the tabulation of AEs and review of laboratory evaluations. AEs, hematological and biochemical toxicity will be classified according to MedDRA 18.1 or later. All demographics, laboratory values, and vital signs will be summarized using descriptive statistics.

10.2 Determination of Sample Size

This is a Phase 1/2 dose escalation and dose expansion study. Cohorts of at least 3 subjects will be treated at each dose level during dose escalation and additional subjects will be added to each dose cohort based on the dose assignment action (escalate to a higher dose, stay at the same dose, or de-escalate to a lower dose) listed in **Table 4** or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. It is estimated that approximately 50 subjects will be enrolled into the dose escalation phase.

Dose Expansion will enroll approximately 50 subjects with RCC. Ongoing safety monitoring will be performed as detailed in Section **10.2.1**.

10.2.1 Expansion Cohorts Safety Monitoring

Bayesian sequential monitoring will be employed to perform ongoing safety monitoring targeting a toxicity rate of not more than 30% (where toxicity follows the same definition as a DLT defined in Section **4.1.2.1**) for the first 80 subjects enrolled in the dose expansion phase. Subjects will be monitored across tumor-specific cohorts after a minimum of 6 subjects treated at the selected dose for the dose expansion phase. The criteria for suspending enrollment due to safety are included in **Table 7** based on Bayesian sequential monitoring designs by **Thall et al. (1995)**. The determination of the criteria is when:

$$\Pr[\text{prob(toxicity)} > 0.30 \mid \text{data}] > 0.95.$$

If there is a greater than 95% chance that the toxicity rate is greater than 30%, then accrual will be suspended and the safety review committee will meet to review safety data including aggregated safety summaries. We assume a beta (0.6, 1.4) prior distribution for the toxicity rate,

which has a mean of 0.3 corresponding to the 30% target toxicity rate. A constant 30% rate was chosen for the standard treatment rate.

Table 7: Suspension Boundaries for Toxicity During Expansion

Total Number of Treated Subjects	Suspending Accrual if ≥ Number of Subjects with Toxicity
1-5	Not Applicable
6-8	5
9-10	6
11-12	7
13-15	8
16-18	9
19-20	10
21-23	11
24-25	12
26-28	13
29-31	14
32-34	15
35-36	16
37-39	17
40-42	18
43-45	19
46-48	20
49-50	21
51-53	22
54-56	23
57-59	24
60-62	25
63-65	26
66-68	27
69-71	28
72-73	29
74-76	30
77-79	31
80	Maximum enrollment for safety monitoring

Table 8: Operating Characteristics for Subject Accrual Suspension Rules

True Toxicity Rate	Accrual Suspension Probability	Achieved Sample Size		
		25th	50th	75th percentiles
0.1	0.001	80	80	80
0.2	0.018	80	80	80
0.3	0.202	80	80	80
0.4	0.759	14	34	80
0.5	0.991	7	14	25
0.6	1.000	6	8	14

An internal safety review committee consisting of representatives from Clinical Development, Drug Safety, Biostatistics, other functional representatives, as needed, and at least one Principal Investigator will meet at least quarterly to review safety data for potential safety risks or more frequently if needed. If it is determined there is a high probability of observing more than 30% toxicities, enrollment will be suspended and the safety review committee will be convened to make a recommendation on the continuation, modification, or discontinuation of the study.

10.3 Replacement of Subjects

Subjects in the dose escalation phase who do not complete Cycle 1 of treatment for reasons other than a DLT will be replaced to provide sufficient number of subjects included for the dose escalation decision. During dose expansion, subjects will not be replaced.

10.4 Analysis Sets

Safety Population: All subjects who receive at least one dose (or partial dose) of study treatment will be included in the analysis of safety.

DLT Population: All subjects who complete at least one cycle of treatment or discontinue from the study treatment due to DLT will be included.

Pharmacokinetic Population: All subjects in the Safety Population who have relatively complete individual analyte concentration-time profiles that allow for the computation of meaningful PK parameter values.

Response Evaluable Population: Subjects who have measurable disease (per RECIST 1.1) at baseline and also have one post-baseline assessment of tumor response or are withdrawn due to progressive disease/death prior to first response assessment.

10.5 Planned Analyses

10.5.1 Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, body weight) and baseline disease characteristics will be tabulated and summarized by dose cohort (for the dose escalation phase) and by tumor type (for the dose expansion phase) and presented in data listings.

10.5.2 Safety

The primary endpoints of the study are to determine the MTD with NKTR-214. Adverse events and toxicity will be evaluated according to NCI CTCAE version 4.03. Safety assessments will be performed by medical review of AEs and laboratory results.

Incidence rate of DLT will be tabulated by dose cohort for the DLT population.

Treatment emergent AEs (TEAEs) within each system will be summarized by preferred term, system organ class, NCI-CTCAE grade of severity, and relationship to the study treatment. Serious AEs and AEs leading to study drug discontinuation will also be summarized.

A TEAE is defined as an AE that was not present prior to treatment with study treatment, but appeared following treatment or was present at treatment initiation, but worsened during treatment. An AE that was present at treatment initiation, but resolved and then reappeared while the subject was on treatment, is a TEAE (regardless of the intensity of the AE when the treatment was initiated).

Vital signs (including change in weight) and clinical laboratory test results will be summarized descriptively by dose (for the dose escalation phase) and by tumor type (for the dose expansion phase). Any significant physical examination findings will be listed. ECG and echocardiogram data will be evaluated by central review and abnormalities, if present, will be listed. A separate listing and summary of all immune-related AEs (irAEs) will be provided. A listing and summary of subjects who discontinued study drug due to an adverse event will be provided.

A data listing for deaths will be provided.

10.5.3 Efficacy

The efficacy outcomes will include:

1. objective response rate (ORR)
2. best overall response (BOR)

[redacted]

4. duration of response (DOR)
5. clinical benefit rate (CBR)
6. time to response (TTR)

[redacted]

The primary efficacy measurement will be ORR per RECIST v1.1 based on the Response Evaluable population by tumor type. The number and proportion of subjects with objective tumor response (CR and PR) will be calculated based on number of subjects with measurable disease at baseline. Ninety-five percent (95%) confidence interval (CI) will also be calculated using exact binomial method. Data listing for tumor assessments and tumor response will be provided.

A secondary measurement will be BOR per RECIST v1.1 based on the Response Evaluable population by tumor type. The number and proportion of subjects with a best overall response of CR or PR will be calculated based on number of subjects with measurable disease at baseline. Ninety-five percent (95%) CI will also be calculated using exact binomial method.

DOR will be defined as the time from first documented CR or PR until the earliest evidence of disease progression, new subsequent anti-cancer therapy, or death from any cause. DOR will be estimated using Kaplan-Meier method for those subjects who have a CR or PR.

Clinical benefit rate will be calculated as the number of subjects with confirmed CR, PR, or SD (where the duration of SD should be $\geq$ 3 months) divided by the total number of subjects in the Response Evaluable Population. The number and proportion of subjects with clinical benefit will be summarized.

The time to response will be summarized descriptively for subjects who have a CR or PR.

[redacted]

[redacted]

10.5.4 Pharmacokinetics

Plasma concentrations of NKTR-214 and its metabolites will be measured using validated method(s). Before analysis of samples, assay sensitivity, specificity, linearity, and reproducibility will be determined. Pharmacokinetic parameters such as C_{max}, time to C_{max} (T_{max}), AUC, CL, V_d, and $t_{½}$ will be estimated from plasma concentration-time data where possible. Pharmacokinetic data from this study may also be pooled with data from other clinical studies for the purpose of pharmacokinetic modeling. Pharmacokinetic parameters will be tabulated and summarized with descriptive statistics. Data from subjects prematurely ending participation in the study may be excluded from the PK data evaluation.

A detailed description of the planned PK analyses will be provided in the PK Analysis Plan.

10.5.5 Immunogenicity

Validated assays will be used for the determination of anti-drug antibodies to NKTR-214 in human serum. Only subjects who receive at least 1 dose of NKTR-214 and provide at least 1 post-treatment sample will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-NKTR-214 antibodies. Samples confirmed positive may also be evaluated for neutralizing antibody activity.

10.5.6 Exploratory Analyses

In addition, characterization of immune system biomarkers (e.g., LDH in melanoma) in predose blood and tumor biopsies, as well as changes in immune system biomarkers after treatment with NKTR-214, and their relationship with efficacy will be exploratory endpoints. Samples may be used for additional research purposes related to the development of NKTR-214.

10.6 Concomitant Medications

All reported concomitant medications will be mapped using the World Health Organization Drug Dictionary. Concomitant medications will be tabulated in summary tables and data listings.

10.7 Missing Data

Statistical considerations and methodology for handling missing data will be detailed in the Statistical Analysis Plan.

11.0 STUDY OR STUDY SITE TERMINATION

The sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

12.0 QUALITY ASSURANCE

Nektar Therapeutics will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

12.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/Independent Ethics Committee (IEC), except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study.

A protocol amendment will be submitted if the sample size will be increased above what is currently specified (or if new cohorts will be added in order to investigate any new dosing schedules, doses, or forms of administration not currently specified in the protocol). All protocol deviations are to be documented and reported to Nektar or its designee.

12.2 Monitoring

In accordance with 21 CFR § 312.56, ICH GCP and local regulations, the clinical monitor will periodically inspect eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR § 312 Subpart D, "Responsibilities of Sponsors and Investigators", ICH GCP and local regulations, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this trial. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug regulations also require the Investigator to allow authorized representatives of the FDA and European Union Regulatory Authorities to inspect and make copies of the same records. The names and identities of the subjects need not be divulged to the Sponsor; however, the records must nevertheless be inspected. This can be accomplished by blacking out the subject's name and replacing the name with the subject's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions prior to initiation of the study.

12.3 Direct Access to Source Data/Documents for Audits and Inspections

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify the Sponsor immediately. The Investigator will ensure that the auditors have access to the clinical supplies, study site facilities; laboratory and that all data (including original source documentation) and all study files are available, if requested.

13.0 ETHICS

This trial will be conducted according to the provisions of the Declaration of Helsinki (October 2008) and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the ICH guidelines on Good Clinical Practice (ICH E6), as well as with any and all applicable federal, state and/or local laws and regulations.

13.1 IRB/IEC Approval

Prior to enrollment of subjects into the study, as required by United States Federal regulations (21 CFR § 56), ICH GCP and local regulations, the protocol and informed consent form will be reviewed and approved by an appropriate IRB or IEC. A letter documenting the IRB or IEC approval must be received by the Sponsor prior to the initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, the Sponsor, or designee will submit a progress report at least once yearly to the IRB or IEC and Regulatory Authorities. The frequency of these reports will depend on local regulations. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC's requirements.

The Investigator, the Sponsor or designee shall promptly notify the IRB or IEC of any SUSARs or any other information that may affect the safe use of the study drug during the course of the trial, per the IRB or IEC's requirements.

13.2 Written Informed Consent

Written informed consent must be obtained from each subject or legal guardian before entering the study. Subjects will be informed of the nature of the study, and the ICF must be presented to each subject in the language in which the subject is fluent.

Informed consent will be obtained and documented from each subject prior to any protocol-specific procedures. Signed and dated ICFs will be retained by the Investigator with the study records. Each subject will be given a copy of the signed consent form.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection Instruments and Source Documents

14.1.1 Study Records

During the study, the Investigator will maintain adequate records for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, eCRFs, signed ICFs, drug accountability records, correspondence with the IRB or IEC and regulatory agencies' AE reports, and information regarding subject discontinuation and completion of the study.

14.1.2 Data Collection Instruments

Data collection instruments (DCIs) (e.g., eCRFs, electronic clinical outcomes assessments [eCOA], and paper forms) will be used in this study. These instruments are used to transmit the information collected during the performance of this study to the Sponsor or Sponsor's designee and regulatory authorities. The Investigator must review the DCIs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the DCIs.

14.2 Retention of Essential Documents

All records and documents pertaining to the study including, but not limited to, those outlined above will be maintained by the Investigator for a period of at least 2 years after FDA/European Medicines Agency (EMA) approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer. In countries outside the United States, at a minimum, records must be kept for the period of time required by the US FDA, and must also comply with the local country regulatory requirements, if longer retention times are required than in the United States. In order to avoid errors, the Investigator will contact the Sponsor before transferring or destroying any study records. The Investigator will also promptly notify the Sponsor in the event of accidental loss or destruction of any study records.

14.3 Confidentiality

Subject confidentiality will be maintained according to local legal and regulatory requirements and applicable US federal regulations and ICH GCP guidelines. In order to comply with GCP guidelines and requirements, subject records will be reviewed during monitoring visits and audits conducted by the Sponsor, Sponsor's representatives, or health authorities. During these activities, every reasonable effort will be made to keep medical information, including subject identifying information, as confidential as possible as required by law.

15.0 PUBLICATION POLICY

All data are the property of the Sponsor. The Sponsor intends that the results of the study will be published and/or presented at scientific meetings. Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Sponsor personnel. In addition, the Sponsor intends to distribute a study report to each Principal Investigator. The Investigator may share this report with subjects who have expressed an interest in knowing the study results.

The Sponsor must receive copies of any intended communication in advance of submission for publication (at least 14 days for an abstract or oral presentation and 30 days for a journal submission). The Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged, and provide any relevant supplementary information.

An Investigator may be required to sign the clinical study report if it is to be used in a registration submission to the health authorities of some countries.

16.0 REFERENCES

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APPENDIX 1: CLINICAL LABORATORY TESTS

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology</th></tr>
<tr><td rowspan="5">• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Red blood cell (RBC) count
• Platelet count
• White blood cell (WBC) count
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)</td><td rowspan="5">• AST (SGOT)
• ALT (SGPT)
• Alkaline phosphatase (ALP)
• Gamma-glutamyl transferase (GGT)
• Albumin
• Creatinine
• Calculated creatinine clearance
• Calcium
• Glucose
• Total protein (TP)
• Total bilirubin
• Sodium
• Potassium
• Chloride
• CO_2 content or bicarbonate
• Blood urea nitrogen (BUN)
• Lactate dehydrogenase (LDH)
• Uric acid</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><td>Additional Labs</td></tr>
<tr><td>• Creatine kinase
• Thyroid stimulating hormone
• Free thyroxine (T4)
• Lipase
• Amylase
• HLA typing (screening only)</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>• Partial thromboplastin time (PTT)
• Prothrombin time (PT)</td></tr>
<tr><th colspan="3">Urinalysis</th></tr>
<tr><td colspan="2">• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocyte esterase
• Blood</td><td>For positive protein, white blood cell or blood, a microscopic examination including:
• Red blood cells
• White blood cells
• Epithelial cells
• Bacteria
• Crystals
• Casts</td></tr>
</table>

Local laboratory will be used for Part 1; central laboratory will be used for Part 2.