Nektar Therapeutics

CLINICAL PROTOCOL

Protocol Number:	20-214-34
Title:	A Multicenter, Phase 1b, Randomized, Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single Dose of Bempegaldesleukin (NKTR-214) Plus Standard of Care versus Placebo Plus Standard of Care in Adults with Mild COVID-19
Version:	Original
Date:	21 September 2020
US IND No.:	152960
Investigational Products:	bempegaldesleukin (NKTR-214)
Indication:	Treatment of SARS-CoV-2 mild infection
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

[redacted]

[redacted]

CONFIDENTIALITY STATEMENT

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee and applicable Regulatory Authorities. Your acceptance of this document constitutes agreement that you will not disclose the information herein to others without written authorization from Nektar Therapeutics except to the extent necessary to obtain informed consent from persons who participate as patients in this study.

PRINCIPAL INVESTIGATOR COMMITMENT

Protocol Number:	20-214-34
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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.

Principal Investigator Signature	**Date**

Printed Name: _____

Institution: _____

Address _____

PROTOCOL APPROVAL PAGE

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Sponsor: Nektar Therapeutics
455 Mission Bay Boulevard South
San Francisco, CA 94158 USA

DocuSigned by:
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LIST OF STUDY CONTACTS

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

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ABBREVIATIONS

Abbreviation or Term	Definition
ACE	angiotensin converting enzyme
ADA	anti-drug-antibodies
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT (SGPT)	alanine transaminase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST (SGOT)	aspartate transaminase (serum glutamic oxaloacetic transaminase)
AUC	area under the concentration-time curve
Bempeg, BEMPEG	abbreviation for bempegaldesleukin, the International Nonproprietary Name (INN) for NKTR-214
Bempegaldesleukin	International Nonproprietary Name (INN) for NKTR-214
bpm	beats per minute
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CRC	Cohort Review Committee
CRF	case report form
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
DCI	data collection instrument
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
ECG	electrocardiogram
ECLA	electrochemiluminescence assay
eCOA	electronic clinical outcomes assessments

Abbreviation or Term	Definition
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOI	end of infusion
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN	interferon
IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-18	interleukin-2, interleukin-3, interleukin-4, interleukin-5, interleukin-6, interleukin-7, interleukin-8, interleukin-10, interleukin-18
IND	Investigational New Drug application
IRB	institutional review board
IRT	Interactive Response Technology
IV	intravenous
kg	kilogram
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
MCP	monocyte chemotactic protein
MDRD	Modification of Diet Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Term	Definition
MERS-CoV	Middle East respiratory syndrome coronavirus
mg	milligram
min	minute(s)
MIP	macrophage inflammatory protein
mL	milliliter
mm Hg	millimeters of mercury
MMWR	Morbidity and Mortality Weekly Report
msec	millisecond
MTD	maximum tolerated dose
NaCl	sodium chloride
NCI	National Cancer Institute
NK	natural killer
NKTR-214	bempegaldesleukin (International Nonproprietary Name)
NOAEL	no observed adverse effect level
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OTC	over-the-counter
PaO_2	partial pressure of arterial oxygen
PaO_2/FiO_2	ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen
PARP	polyadenosine diphosphate ribose polymerase
PBMC	peripheral blood mononuclear cell
PD-L1	programmed cell death ligand 1
PE	pulmonary embolism
PEG	polyethylene glycol
PK	pharmacokinetic
q3w	every 3 weeks
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
R	randomization
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or Term	Definition
rhIL-2	recombinant human interleukin-2
RT-PCR	reverse transcription polymerase chain reaction
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2, the virus causing COVID-19
SIRS	systemic inflammatory response syndrome
SOC	standard of care
SOP	standard operating procedure
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
Treg	regulatory T cell
ULN	upper limit of normal
US, USA	United States of America
WFI	Water for Injection
WHO	World Health Organization
WOCBP	Women of childbearing potential

1.0 STUDY SYNOPSIS

<table>
<tr><td>Title of Study:</td><td>A Multicenter, Phase 1b, Randomized, Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single Dose of Bempegaldesleukin (NKTR-214) Plus Standard of Care versus Placebo Plus Standard of Care in Adults with Mild COVID-19</td></tr>
<tr><td>Sponsor:</td><td>Nektar Therapeutics</td></tr>
<tr><td>Name of Finished Product(s):</td><td>Bempegaldesleukin (NKTR-214 drug product)</td></tr>
<tr><td>Name of Active Ingredient (s):</td><td>Bempegaldesleukin (NKTR-214) drug substance</td></tr>
<tr><td>Phase of Development:</td><td>Phase 1b</td></tr>
<tr><td>Objectives:</td><td>The primary objectives are:
• To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of bempegaldesleukin plus standard of care (referred to in this document as bempegaldesleukin/SOC) compared with placebo plus standard of care (referred to in this document as placebo/SOC) in patients with mild COVID-19 (coronavirus disease 2019; SARS-CoV-2).
• To evaluate the safety and tolerability of bempegaldesleukin administered as a single intravenous (IV) dose and to define the recommended Phase 2 dose (RP2D) of bempegaldesleukin in patients with mild COVID-19.
• To assess the effect of bempegaldesleukin on the time course and extent of changes in absolute lymphocyte counts.
Secondary objectives:
The secondary objectives listed below involve comparison of bempegaldesleukin/SOC versus placebo/SOC in patients with mild COVID-19:
• To estimate the incidence of adverse events (AEs).
• To evaluate the frequency of serious AEs (SAEs).
• To determine the percentage of patients who require supplemental oxygen.
• To evaluate clinical status based on the World Health Organization (WHO) Clinical Progression Scale. This will be determined once more information is obtained about the clinical meaning/interpretation. The scale is as follows:
<table>
<tr><th>Patient state</th><th>Descriptor</th><th>Score</th></tr>
<tr><td>Uninfected</td><td>Uninfected; no viral RNA detected</td><td>0</td></tr>
<tr><td rowspan="3">Ambulatory mild disease</td><td>Asymptomatic; viral RNA detected</td><td>1</td></tr>
<tr><td>Symptomatic; independent</td><td>2</td></tr>
<tr><td>Symptomatic; assistance needed</td><td>3</td></tr>
<tr><td rowspan="2">Hospitalized: Moderate disease</td><td>Hospitalized, no oxygen therapy[a]</td><td>4</td></tr>
<tr><td>Hospitalized; oxygen by mask or nasal prongs</td><td>5</td></tr>
<tr><td rowspan="4">Hospitalized: Severe disease</td><td>Hospitalized; oxygen by non-invasive ventilation or high-flow</td><td>6</td></tr>
<tr><td>Intubation and mechanical ventilation, $PaO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$</td><td>7</td></tr>
<tr><td>Mechanical ventilation, $PaO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors</td><td>8</td></tr>
<tr><td>Mechanical ventilation, $PaO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO</td><td>9</td></tr>
<tr><td>Dead</td><td>Death</td><td>10</td></tr>
</table>
Abbreviations: ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen; SpO_2 = oxygen saturation
a. If hospitalized for isolation only, record status as for ambulatory patient.
Source: WHO 2020</td></tr>
</table>

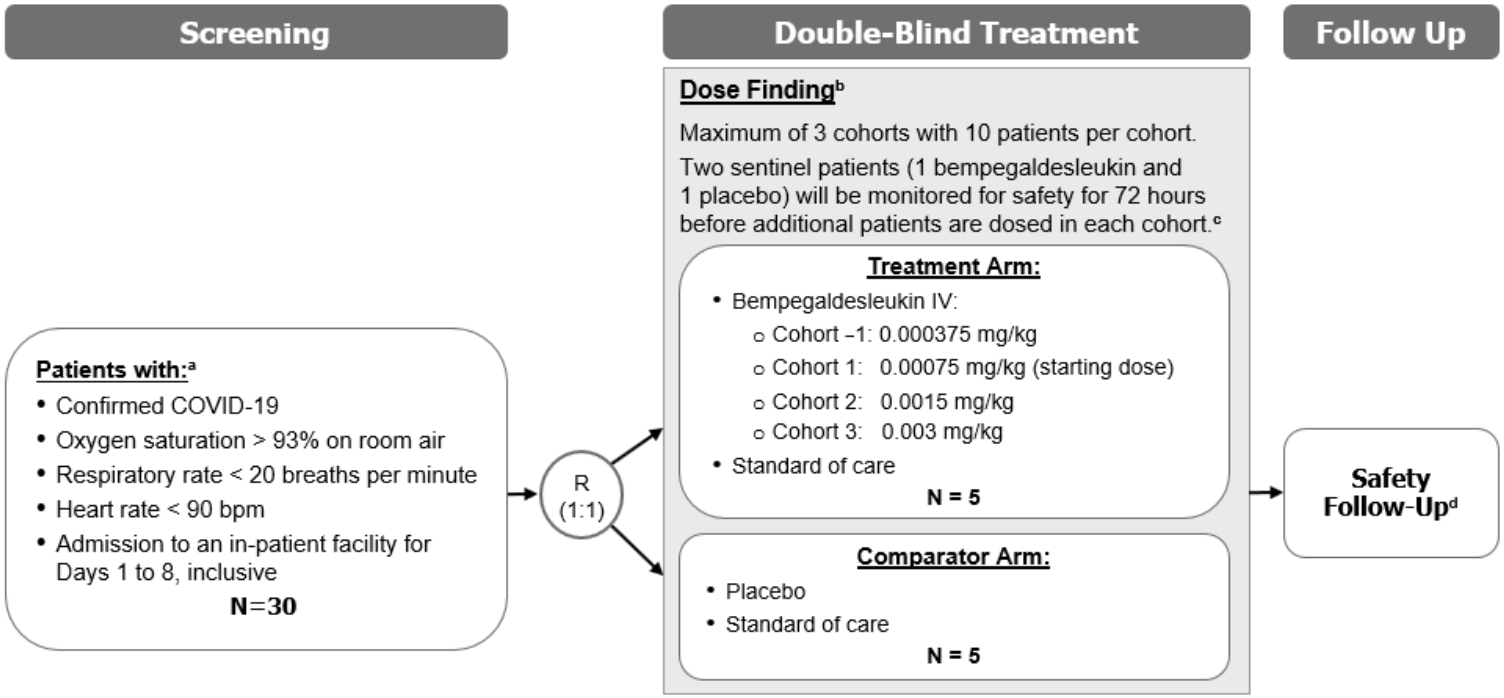
	• To assess the immunologic effects in blood before and after study drug administration, including effects on cytokines, natural killer cells, T-cells, and other serum proteins and immune modulators.
Duration of Treatment:	Patients will be treated with 1 dose of bempegaldesleukin or placebo in combination with SOC for COVID-19.
Study Population:	Adults aged 18 years and older with mild COVID-19.
Number of Patients (Planned):	Approximately 30 patients.
Number of Study Sites:	Up to 10 sites
Countries:	United States
Study Design:	This is a multicenter, Phase 1b, randomized double-blind, placebo-controlled trial to assess the safety, tolerability pharmacokinetics, and pharmacodynamics of bempegaldesleukin/SOC in adults with mild COVID-19, as well as to determine the RP2D of bempegaldesleukin. During the study, patients will receive 1 dose of bempegaldesleukin or placebo and must remain in the hospital or be admitted to an in-patient facility for monitoring until at least Day 8. Patients will be randomized (1:1 ratio) in groups of 10 patients (5 bempegaldesleukin/SOC and 5 placebo/SOC) in each cohort to receive one IV infusion of bempegaldesleukin in combination with standard of care or one IV infusion of placebo in combination with standard of care. Eligible patients will be enrolled into 1 of 3 dose cohorts with doses ranging from 0.00075 mg/kg to 0.003 mg/kg. The first two patients randomized and treated in each dose cohort (1 with bempegaldesleukin/SOC and 1 with placebo/SOC) will serve as sentinel patients. Enrollment in each cohort will be staggered as follows. A Cohort Review Committee (CRC) will monitor blinded safety and tolerability data for the first 72 hours after study drug administration from the 2 sentinel patients before additional patients in that cohort are treated. If the CRC determines additional patients may be randomized, 2 patients will be randomized (1 with bempegaldesleukin/SOC and 1 with placebo/SOC), treated with study drug, and observed for 72 hours. For every 2 patients, the Medical Monitor will review the blinded safety and tolerability data for the first 72 hours after study drug administration to determine if the next 2 patients may be randomized. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the Medical Monitor will request a review of the safety data by the CRC. After 10 patients have completed a 7-day observation period for dose-limiting toxicity (DLT; see Section 5.3.2.1 for additional details), the CRC will assess the accumulated, blinded safety and tolerability data, as well as any available pharmacokinetic, pharmacodynamic, and disease measurement data, to determine whether dose escalation or de-escalation from the tested bempegaldesleukin dose level is warranted. This decision will be based on blinded data using pre-defined criteria, including the proportion of patients who experience a DLT (see Section 5.3.1). Patients who drop out of the study for reasons other than a DLT, before the DLT evaluation period (Days 1 to 7) has elapsed, may be replaced. The RP2D of bempegaldesleukin in patients with mild COVID-19 will be based on the totality of safety, tolerability, pharmacokinetic, pharmacodynamic, and disease measurement data.

Key Eligibility Criteria:	The following list contains key eligibility criteria only; a full list of eligibility criteria is provided in Section 4.0. **Key Inclusion Criteria:** • Provide written, informed consent to participate in the study and follow the study procedures. • Male or female patients, age 18 years or older on the day of signing the informed consent form. • Agrees to admission to an in-patient facility for monitoring from Days 1 to 8, inclusive. • Symptoms of mild illness with COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms) without shortness of breath, dyspnea, or clinical signs indicative of more serious COVID-19. • Confirmed COVID-19 determined by a positive, documented SARS-CoV-2 infection determined by a commercial or public health assay in any specimen within 4 days prior to the screening visit or during the 7-day screening period. • Respiratory rate < 20 breaths per minute, heart rate < 90 beats per minute (bpm). • Oxygen saturation by pulse oximetry > 93% on room air. • Body mass index < 35 kg/m^2. • Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min. • Alanine transaminase (ALT) or aspartate transaminase (AST) < 2 × upper limit of normal (ULN) and total bilirubin < 1.5 × ULN. • Agrees to not participate in another clinical trial for the treatment of COVID-19 while on study unless the patient's condition has worsened and is considered to be moderate, severe, or critical by the Investigator. **Key Exclusion Criteria:** • Shortness of breath, hypoxia (ie, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] ≤ 300 mm Hg), or signs of serious lower airway disease. • C-reactive protein, lactate dehydrogenase (LDH), or interleukin-6 (IL-6) > 1.5 × ULN. • D-dimer or ferritin > 1.5 × ULN. • Imminently requiring, or currently on, mechanical ventilation or extracorporeal membrane oxygenation (ECMO). • Systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg. • Evidence of acute respiratory distress syndrome (ARDS) or systemic inflammatory response syndrome (SIRS)/shock. • Known cardiovascular history, including unstable or deteriorating cardiac disease. • Autoimmune disease. • History of pulmonary embolism (PE), deep vein thrombosis (DVT), or prior clinically significant venous or non-cerebrovascular accident/transient ischemic attack arterial thromboembolic event. • Central nervous system disease or evidence of central nervous system dysfunction. • History of pulmonary disease, including cystic fibrosis. • Requirement for > 2 anti-hypertensive medications. • Unwilling to refrain from alcohol consumption from Day 1 of admission to the in-patient facility until discharge from the facility. • Adrenal insufficiency.

Product Dose and Mode of Administration for:	**Test Product**: The starting dose of bempegaldesleukin will be 0.00075 mg/kg IV.
	Comparator Product: Placebo control will consist of sterile normal saline solution administered at the same volume as the active administration.
	Standard of Care: All patients will receive the standard of care for COVID-19 determined by the Investigator or institution, which should follow the approved prescribing guidelines in their country and institution.
Pharmacodynamics and Biomarkers:	Blood samples for analyses of absolute lymphocyte counts, DNA/RNA sequencing, SARS-CoV-2 serology, immune cell profiling, including profiling of SARS-CoV-2 specific T cells, and cytokines will be collected. Detection of SARS-CoV-2 nucleic acid in respiratory specimens will be measured using oropharyngeal swabs and anterior nares or nasopharyngeal swabs collected in a manner consistent with the Centers for Disease and Control (CDC) specimen collection guidelines (CDC 2020b). Samples will be collected at various scheduled sample times from predose to the 30-day follow-up visit (see Section 1.2).
Pharmacokinetic and Immunogenicity Evaluation:	Blood samples for pharmacokinetic and immunogenicity will be collected from patients at multiple scheduled sampling times during the study. Validated methods will be used to measure plasma concentrations of bempegaldesleukin. Pharmacokinetic parameters such as maximum concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration-time curve (AUC) will be estimated from plasma concentration-time data where possible. Validated methods will be used to measure anti-drug antibodies and their ability to neutralize bempegaldesleukin.
Safety Evaluation:	Assessment of safety will be determined by an ongoing review of the following: • AEs, including treatment-emergent AEs, incidence of treatment-related AEs, SAEs, and death. • The AE of special interest, cytokine release syndrome (CRS). • Clinical laboratory tests (blood and urine sampling). • Vital signs. • Physical examination.
Disease Measurement:	The disease measurements are: • The percentage of patients who require supplemental oxygen. • Change from baseline based on the daily collection of the WHO Clinical Progression Scale.
Statistical Methods	**General Considerations:** In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients. **Safety:** Safety assessments will include AEs, clinical laboratory tests, and vital signs. All safety data will be summarized for the safety population using descriptive statistics. **Pharmacodynamics**: The fold change from baseline at each evaluation time and the maximum fold change of absolute lymphocyte counts achieved will be summarized by treatment (bempegaldesleukin/SOC or placebo/SOC). **Disease Measurement:** Disease measurement will be summarized by treatment group for the safety population using descriptive statistics.

1.1 Study Schematic

Figure 1: Study Schematic



Abbreviations: bpm = beats per minute; CRC = Cohort Review Committee; COVID-19 = coronavirus disease 2019 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]); IV =intravenous; R = randomization; RP2D = recommended Phase 2 dose; SOC = standard of care

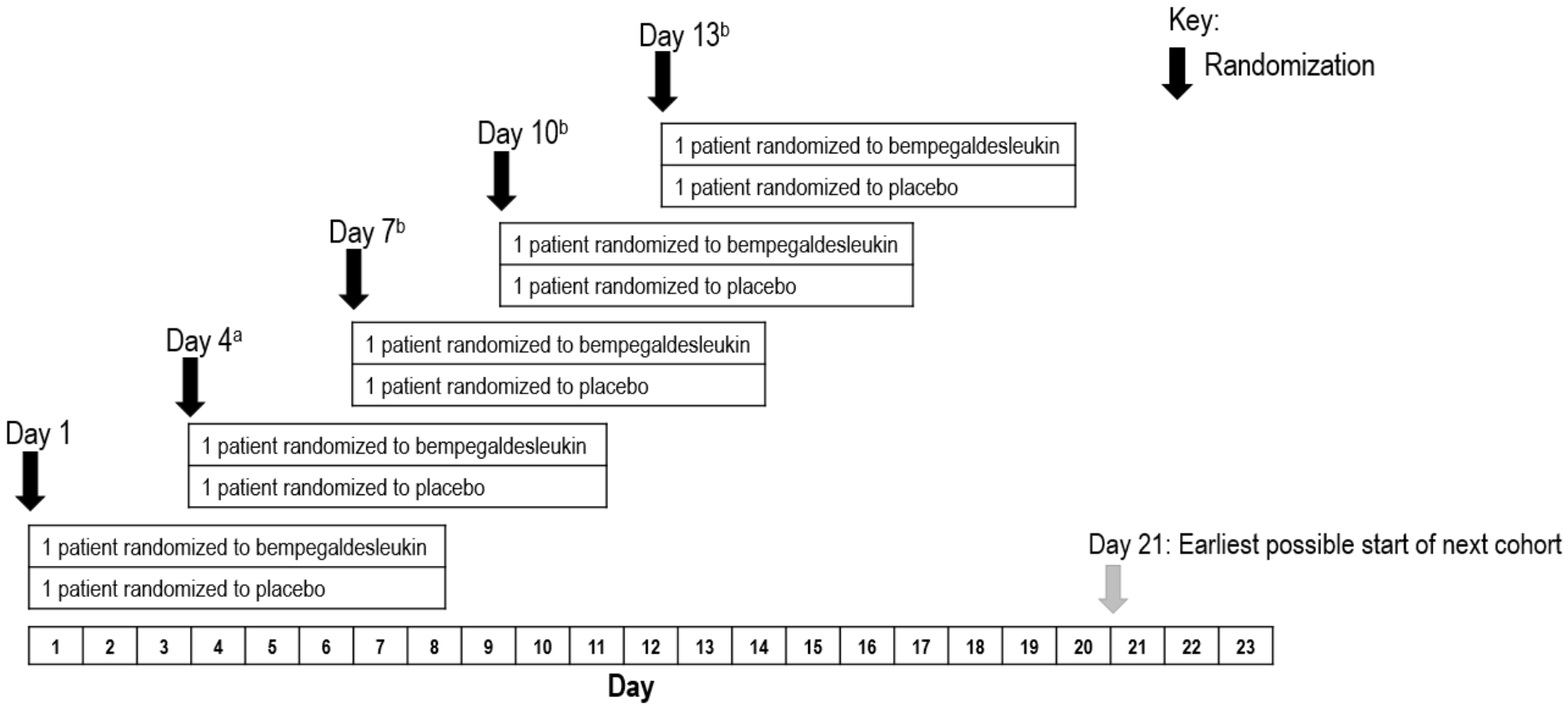
a. Patients will be evaluated for enrollment during the up to 7-day screening period. The complete list of entry criteria is provided in Section 4.0.

b. A CRC will review blinded safety, tolerability, pharmacokinetic, pharmacodynamic, and disease measurement data, make decisions about escalating or de-escalating the bempegaldesleukin dose, and identify the RP2D (see Section 7.16).

c. If the CRC determines additional patients may be randomized, 2 patients will be randomized (1 with bempegaldesleukin/SOC and 1 with placebo/SOC), treated with study drug, and observed for 72 hours. For every 2 patients, the Medical Monitor will review the blinded safety and tolerability data for the first 72 hours after study drug administration to determine if the next 2 patients may be randomized (Section 5.3).

d. The Safety Follow-Up should occur 30 days (± 7 days) after discharge from the hospital or in-patient facility. See Section 5.7 for additional details.

Figure 2: Dose Cohort Schematic



Note. The Safety Follow-Up should occur 30 days (± 7 days) after discharge from the hospital or in-patient facility. See Section 5.7 for additional details.

a. Earliest possible randomization day for the next eligible patients if approved by CRC (see Section 5.3).

b. Earliest possible randomization day for the next eligible patients if approved by Medical Monitor (see Section 5.3).

1.2 Schedule of Events

Table 1: Schedule of Events

Procedure / Period:	Screening	Treatment		Post-Treatment
Study Days[a]:	Days −7 to −1	Day 1	Days 2+ until Discharged[a]	Safety Follow-Up 30 days after discharge (± 7 days)
Informed consent	X			
Inclusion/ exclusion criteria, including documentation of positive SARS-CoV-2 infection	X			
Medical history	X			
Randomization		Predose		
Physical examination[b]	X	Predose	Every day	
Vital signs, including SpO_2[c]	X	Predose	Every day	
ECG[d]	X			
Clinical data collection[e]		Predose	Every day	Call to patient[r]
Laboratory Assessments[f]				
Hematology and chemistry[g]	X (local lab)	Predose[h] (central lab)	Days 2, 3, 4, 6, 8 (central lab)[j]	
Coagulation[g]	X (local lab)	Predose[h] (central lab)		
Additional laboratory assessments	X (IL-6: local or central lab; other assessments: local lab)	Predose[h] (central lab)		
Serology HIV/HBV/HCV	X (local lab)			
Pregnancy test[k]	X (local lab)		Day 8 (local lab)[j]	
Urinalysis (dipstick)		Predose[h] (local lab)		
PK assessments[l]		Predose[h] and EOI[i]	Days 2, 3, 4, 6, 8[j]	
Immunogenicity assessments[l]		Predose[h]	Day 8[j]	Collect sample[s]

Schedule of assessments continued on next page.

Table 1: Schedule of Events (Contd)

Procedure / Period:	Screening	Treatment		Post-Treatment
Study Days[a]:	Days −7 to −1	Day 1	Days 2+ until Discharged[a]	Safety Follow-Up 30 days after discharge (± 7 days)
Biomarkers (central laboratory only)				
Respiratory specimens for detection of SARS-CoV-2 nucleic acid[m,n]		Predose[h]	Days 4 and 8[j]	Collect sample[s]
SARS-CoV-2 serology[m]		Predose[h]	Days 4 and 8[j]	Collect sample[s]
HLA Haplotyping[m]		Predose[h]		
DNA/RNA sequencing[m]		Predose[h]	Days 4 and 8[j]	Collect sample[s]
Immune cell profiling[m]		Predose[h]	Day 8[j]	Collect sample[s]
Cytokine assessments[m]		Predose[h]	Days 2, 3, 4, 6, 8[j]	
Study Drug Administration				
Study drug administration[o]		X		
Hydration		X[p]	Days 2-4[p]	
Standard of care[q]		As clinically indicated		
AE assessment	X	X	X[t]	Call to patient[r]
Review of concomitant medications	X	X	X[t]	Call to patient[r]

Abbreviations: AE = adverse events; ECG = electrocardiogram; EOI = end of infusion; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation

a. Patients must remain in the hospital or be admitted to an in-patient facility for monitoring until at least Day 8. Study assessments may be delayed or moved ahead of the window to accommodate unforeseen delays after permission from the Medical Monitor. All procedures and examinations should be performed before the administration of study drug, except as indicated.

b. Physical examination will include a full physical examination at Screening and on Day 1 (prior to dosing) and targeted physical exams on other days; see Section 7.13.

c. Vital sign assessments for Day 1 must occur prior to administering study drug. See Sections 5.5.4.1 and 7.14.

d. ECG must be done within 7 days prior to Day 1. See Section 7.15.

e. Clinical data to be collected include:
   - Clinical support measures (eg, oxygen requirement) and physical activity limitations, see Section 8.1.1.
   - WHO Clinical Progression Scale, see Section 8.1.2.

Laboratory Assessments and Biomarkers:

f. Safety laboratory assessments are categorized in two groups depending on the purpose:
   - For local laboratory assessments collected in this study, see Appendix 1A.
   - For central laboratory assessments collected throughout the study, see Appendix 1B.

g. Hematology, serum chemistry, and coagulation assessments should be drawn in the morning.

h. Predose samples should be collected up to 3 hours before study drug administration.

i. End of infusion samples should be collected within 30 minutes of the end of study drug infusion.

j. If the patient is discharged from the in-patient facility prior to Day 6, a sample will be collected between Days 6 to 10, inclusive. If the patient is unable to return to the clinic, samples may be collected by research staff or designee at an alternate location.

k. See Section 7.11.1.

l. See Section 5.10.

m. All biomarker samples should be drawn in the morning. See Section 5.11 for additional details.

n. Collect oropharyngeal and anterior nares or nasopharyngeal swabs according to the CDC guidelines (CDC 2020b).

Study Drug Administration:

o. See Sections 5.5.1 and 5.5.2 for additional details.

p. Patients should receive IV fluid as tolerated on the day of dosing (Day 1) and continue with oral hydration as tolerated for the subsequent 3 days. In the event patients cannot adhere to the oral hydration guidelines, IV hydration should be administered as clinically indicated. If the patient is prematurely discharged from the in-patient facility before Day 4, contact the patient (by telephone or clinic visit) once between Days 2 to 4, inclusive, to remind the patient of the oral hydration guidelines and to assess for any symptomatology and compliance with the hydration guidelines. Site personnel must document the hydration and the results of the discussion. Additionally, advise patients who are discharged from the in-patient facility before Day 8:
   - To restrain from activities that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) from Days 1 to 8.
   - If experiencing orthostatic symptoms, the patient should contact site personnel and consider increasing oral hydration.

   See Section 5.5.4.2 for additional details.

q. See Section 5.5.3 for additional details.

r. The Safety Follow-Up call should occur 30 days (± 7 days) after discharge from the hospital or in-patient facility. If the patient remains at the in-patient facility after Day 8, the Safety Follow-Up call should occur no later than 38 days (± 7 days) after Day 1, the day of study drug administration. See Section 5.7 for additional details.

s. Samples will be collected 30 days (± 7 days) after hospital or in-patient facility discharge for immunogenicity, DNA/RNA sequencing, SARS-CoV-2 serology, immune cell profiling, and detection of SARS-CoV-2 nucleic acid. Note:
   - If the patient is unable to return to the clinic, samples may be collected by research staff or designee at an alternate location.
   - If the patient remains at the in-patient facility after Day 8, samples should be collected no later than 38 days (± 7 days) after Day 1, the day of study drug administration.

   See Section 5.7 for additional details.

t. If the patient is prematurely discharged from the in-patient facility, site personnel should contact the patient by telephone each day until Day 8 for collection of AEs and concomitant medications.

2.0 INTRODUCTION

2.1 Background

2.1.1 COVID-19

Following the outbreak of severe acute respiratory syndrome (SARS) in 2002, human coronaviruses have been reported as pathogens that cause severe symptoms in respiratory tract infections. A human coronavirus isolated from the respiratory epithelium of unexplained pneumonia patients in Wuhan, China in December 2019, initially named "2019 novel coronavirus" (2019-nCoV) and later designated "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), causes acute lung symptoms, leading to a condition that has been named "coronavirus disease 2019" (COVID-19) (Xu 2020).

2.1.1.1 Clinical Presentation of Patients with Mild COVID-19

COVID-19 shows similarities with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) infections (Gralinski 2020). Most cases of COVID-19 reported to date are of mild severity. In China, up to 81% of patients were reported to have mild disease, however, this estimate includes a range of disease severity from asymptomatic to mild pneumonia (Wu 2020). Among the COVID-19 cases reported to the Centers for Disease and Control (CDC) from January 22 to May 30, 2020, 14% of patients were hospitalized, 2% were admitted to an intensive care unit, and 5% died. Excluding the 4% of patients who were asymptomatic, approximately 75% of patients in the US would be expected to have mild disease (Stokes 2020). Symptoms of mild COVID-19 include fever, cough, sore throat, malaise, headache, muscle pain, and gastrointestinal symptoms, without shortness of breath or dyspnea (FDA 2020). The clinical course may rapidly progress for some patients with mild COVID-19, especially for patients with risk factors for severe disease (CDC 2020a; Guan 2020; Huang 2020). Worsening of patient clinical status has been observed approximately 5 to 8 days after the onset of COVID-19 symptoms (Kujawski 2020; Huang 2020; Guan 2020; Kim 2020). In severe cases of COVID-19, the disease can cause pneumonia, severe acute respiratory syndrome, multi-organ failure, and death (FDA 2020).

2.1.2 Bempegaldesleukin (NKTR-214) for Patients who have Mild COVID-19

Bempegaldesleukin (NKTR-214) is an engineered interleukin-2 (IL-2) cytokine prodrug that provides a controlled and sustained IL-2 signal to T cells and natural killer cells. Upon administration to patients with cancer, we observed increased number and proliferation of T cells and natural killer cells (see Section 2.1.3.1), and concurrent increases in cytolytic effector molecules such as granzyme B in tumor (Bentebibel 2019). To overcome a COVID-19 infection, an innate and most importantly adaptive (T cell-mediated) immune response to the virus is required, which has been observed in surviving patients (Tan 2020a; Zheng 2020; Zhou 2020; Ma 2020 [preprint]). Lymphopenia has been identified as biomarker of COVID-19 disease severity (Richardson 2020; Tan 2020a; Ruan 2020; Zhou 2020; Yang 2020a; Thevarajan 2020; Chen 2020; Wang 2020). We are conducting this Phase 1b study to evaluate if

bempegaldesleukin can be administered safety to patients with mild COVID-19 to maintain normal or increase lymphocytes. The ultimate long-term goal of the development program is to determine if bempegaldesleukin can overcome lymphopenia in patients hospitalized for COVID-19 by correcting both the numerical and functional impairment of lymphocytes to improve survival.

2.1.3 Bempegaldesleukin (NKTR-214) Polymer Conjugation Design

Bempegaldesleukin was designed to mitigate the severe toxicities associated with administration of IL-2 (aldesleukin, Proleukin®). While aldesleukin is a well-established cytokine therapy first approved by the United States Food and Drug Administration (FDA) in 1992 for the treatment of metastatic renal cell carcinoma (RCC) and subsequently for the treatment of metastatic melanoma, aldesleukin has multiple shortcomings. These challenges include rapid clearance (> 95% clearance within 30 minutes), which necessitates frequent administration of high doses and resultant increased severe toxicity that led the FDA to issue a black-boxed warning (Proleukin 2018). The warning alerts clinicians and patients that aldesleukin administration has been associated with capillary leak syndrome, which may result in hypotension and reduced organ perfusion that may be severe and can result in death.

The goal of engineering bempegaldesleukin as a pegylated form of IL-2 was to reduce the treatment-limiting toxicities of aldesleukin, prolong the half-life, and ultimately enhance efficacy. The differences between aldesleukin and bempegaldesleukin are presented in Table 2.

Table 2: Comparison of Aldesleukin to Bempegaldesleukin

Parameter	Aldesleukin (Proleukin)[a]	Bempegaldesleukin
Structure	Human recombinant IL-2.	Pegylated human recombinant IL-2.
Dosing	IV infusion every 8 hours for 5 consecutive days.	IV infusion every 2-3 weeks.
Administration	Hospital setting. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.	Outpatient setting[b].
Half-life	85 minutes	20 hours
Primary life-threatening AEs requiring hospital monitoring	• Capillary leak syndrome. • Cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes. • Impaired neutrophil function and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis.	Primary life-threatening toxicities associated with aldesleukin have not been observed.

a. Proleukin 2018.

b. Bempegaldesleukin is administered in an outpatient setting when used as an immuno-oncology agent, as safety and tolerability have been evaluated in patients with advanced cancers. However, hospitalization or admission to an in-patient facility through Day 8 is required in Study 20-214-34 because safety and tolerability have not yet been evaluated in patients with COVID-19 (see Section 2.2.3).

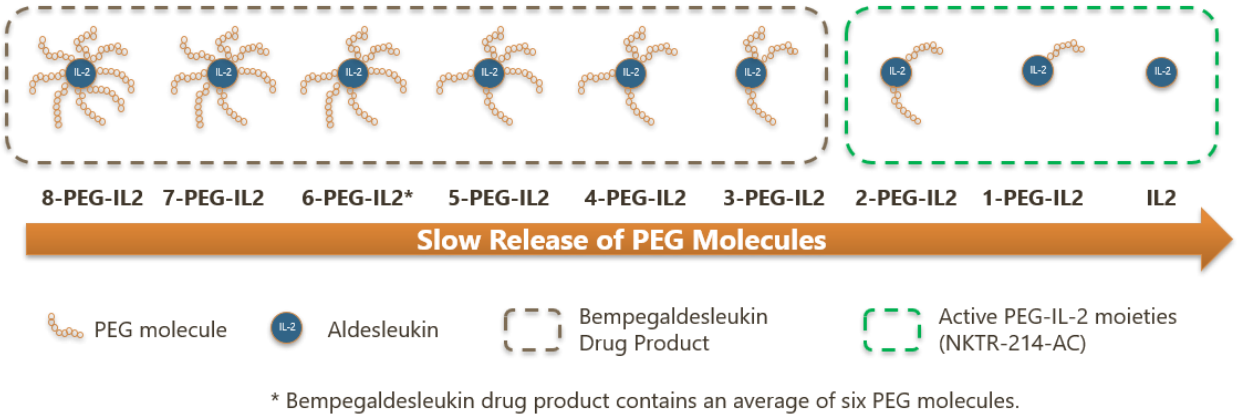
To date, bempegaldesleukin has been studied as an immunotherapeutic agent in different oncology indications in > 600 patients with a well-tolerated safety profile that allows for outpatient administration of the compound. The majority of AEs observed have been mild to moderate in severity, transient and typically resolve in 2-4 days following study drug administration. Bempegaldesleukin has been routinely administered to cancer patients at 0.006 mg/kg and nivolumab 360 mg q3w. In Study 20-214-34, a single dose of bempegaldesleukin will be administered to adults with mild COVID-19 at a starting dose of 0.00075 mg/kg; this starting dose is one-eighth of the 0.006 mg/kg dose that is commonly used in the oncology setting in combination with other agents and is one-twelfth of the maximum tolerated dose (MTD) for monotherapy (ie, 0.009 mg/kg; see Section 2.1.4.2.1) in late stage cancer.

2.1.3.1 Bempegaldesleukin Mechanism of Action, Pharmacokinetics and Pharmacodynamics

Bempegaldesleukin is an immunotherapeutic protein prodrug with unique properties specifically designed to activate the immune system by providing a controlled, sustained signal to the IL-2 receptor pathway.

Bempegaldesleukin contains aldesleukin conjugated to 3 to 8 polyethylene glycol (PEG) groups, with an average of 6 PEG groups per aldesleukin. In this fully pegylated prodrug form, bempegaldesleukin is inactive. After administration in vivo, PEG groups release to form various PEG-IL-2 species composed of releasable and stable PEG groups. Active cytokines are composed of releasable and stable 2-PEG-IL-2, releasable and stable 1-PEG-IL-2, and IL-2 (Figure 3) that have a peak plasma concentration 26 to 48 hours after infusion.

Figure 3: Release of PEG Groups from Bempegaldesleukin to Form Active Cytokines



* Bempegaldesleukin drug product contains an average of six PEG molecules.

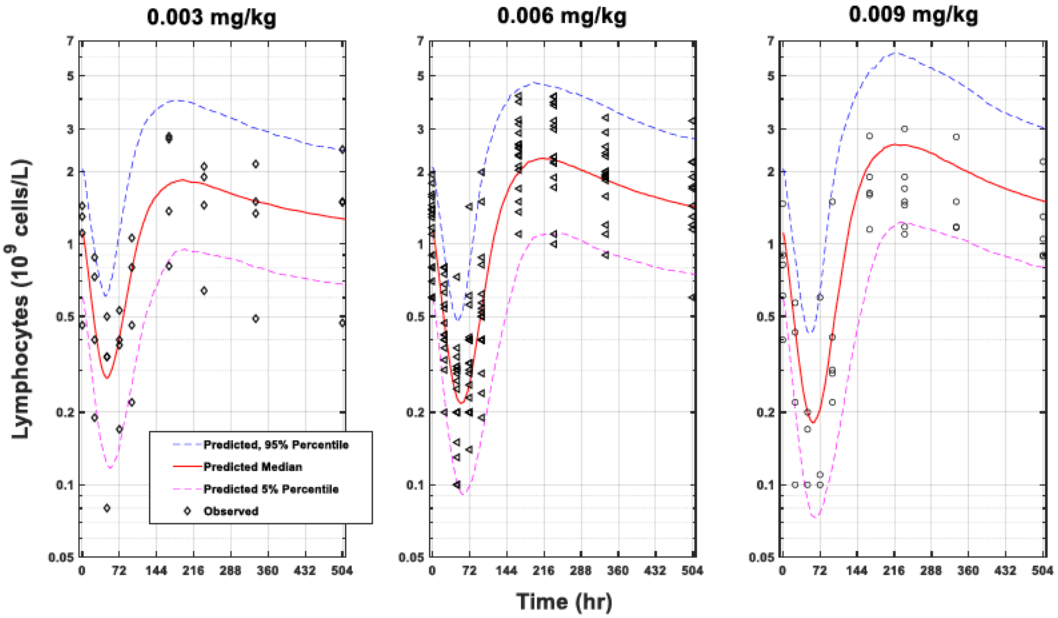
The slow generation of the 2-PEG-IL-2 and 1 PEG-IL-2 significantly mitigates the rapid-onset of systemic cytokine-related toxicities associated with high dose IL-2. In vitro hydrolysis studies demonstrate PEG release occurs sequentially, with a half-life of 20 hours for each step in the release, supporting the lack of a “burst” IL-2 release (Charych 2016). Therefore, slow release of

PEG relative to fast clearance of IL-2 results in predominant exposure to active pegylated IL-2 conjugates.

While pegylated IL-2 conjugates are the predominant moieties in plasma following bempegaldesleukin dosing, exposure to free IL-2 is very low. In a study of 28 patients receiving bempegaldesleukin monotherapy over a dose range of 0.003 to 0.012 mg/kg, due to the slow and gradual release of PEG molecules after administration of bempegaldesleukin relative to the fast clearance of IL-2, plasma concentrations of free IL-2 were only sporadically detected in 76 of 425 samples, with free IL-2 concentrations ranging from 0.509 to 4.44 ng/mL (one sample at 19.4 ng/mL) (Study 15-214-01 [EXCEL]). After administration of 0.003 mg/kg bempegaldesleukin, free IL-2 was detected in 4 of 645 samples. IL-2 concentrations in the four samples with undetectable levels ranged between 0.6 to 1.3 ng/mL. Hence, exposure to free IL-2 is low after administration of bempegaldesleukin. In contrast, reported IL-2 levels in patients with COVID-19 tended to remain below approximately 35 pg/mL at all stages of the disease (Diao 2020; Han 2020; Huang 2020; Liu 2020; Long 2020; Shi 2020; Tan 2020b; Yang 2020b).

In cancer patients, bempegaldesleukin monotherapy promoted dose-dependent elevations of lymphocyte levels over the range of doses tested, 0.003 to 0.012 mg/kg (Figure 4; Table 3). Based on pharmacokinetic/pharmacodynamic (PK/PD) modeling, lymphocyte increases are also predicted to occur at bempegaldesleukin doses below this range. Lymphocyte kinetics after administration of bempegaldesleukin are similar to those described after administration of IL-2 and include initial activation and relocation to tissue, resulting in a transient decrease in lymphocytes on Day 3, followed by a systemic increase with lymphocyte levels reaching approximately 2-fold those observed at baseline between Days 8 and 11. Further characterization of immune cells on Day 8 confirmed increased numbers of CD4, CD8, and natural killer cells, with increased proliferation (Figure 5). Increases in lymphocytes were observed across the clinical development program of bempegaldesleukin, independent of patient age, as illustrated for patients treated with bempegaldesleukin and nivolumab in Figure 6.

Figure 4: Bempegaldesleukin Monotherapy Increases Absolute Lymphocyte Counts in Patients with Cancer



Symbols represent observed lymphocyte counts in Study 15-214-01. Observed data were fit with a PK/PD model, which was used to simulate 1000 patients to obtain median with 5% and 95% percentile lymphocyte counts by dose.

Table 3: Bempegaldesleukin Increases Absolute Lymphocyte Counts in Patients with Cancer

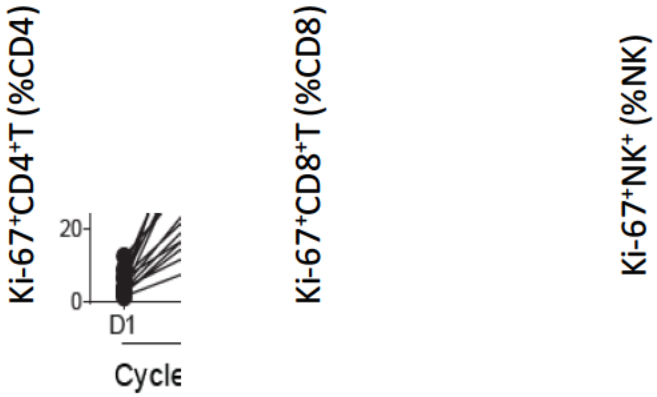
Parameter	Bempegaldesleukin Dose and Simulated (Median [5, 95% Percentile]) Absolute Lymphocyte Counts (× 10^9 cell/mL)[a]					
	0.003 mg/kg		0.006 mg/kg		0.009 mg/kg	
	Baseline	Maximum	Baseline	Maximum	Baseline	Maximum
ALC	1.10 (0.599, 2.05)	1.95 (0.976, 4.20)	1.11 (0.595, 2.08)	2.44 (1.24, 5.13)	1.11 (0.587, 2.05)	2.89 (1.35, 6.72)
Increase in ALC	1.77-fold		2.20-fold		2.60-fold	

Abbreviation: ALC = absolute lymphocyte count

a. Observed bempegaldesleukin and lymphocyte concentrations were fit with a PK/PD model and 1000 patients were simulated to obtain median, 5% and 95% absolute lymphocyte counts at baseline and at the time of maximum counts.

Source: Study 15-214-01 (EXCEL)

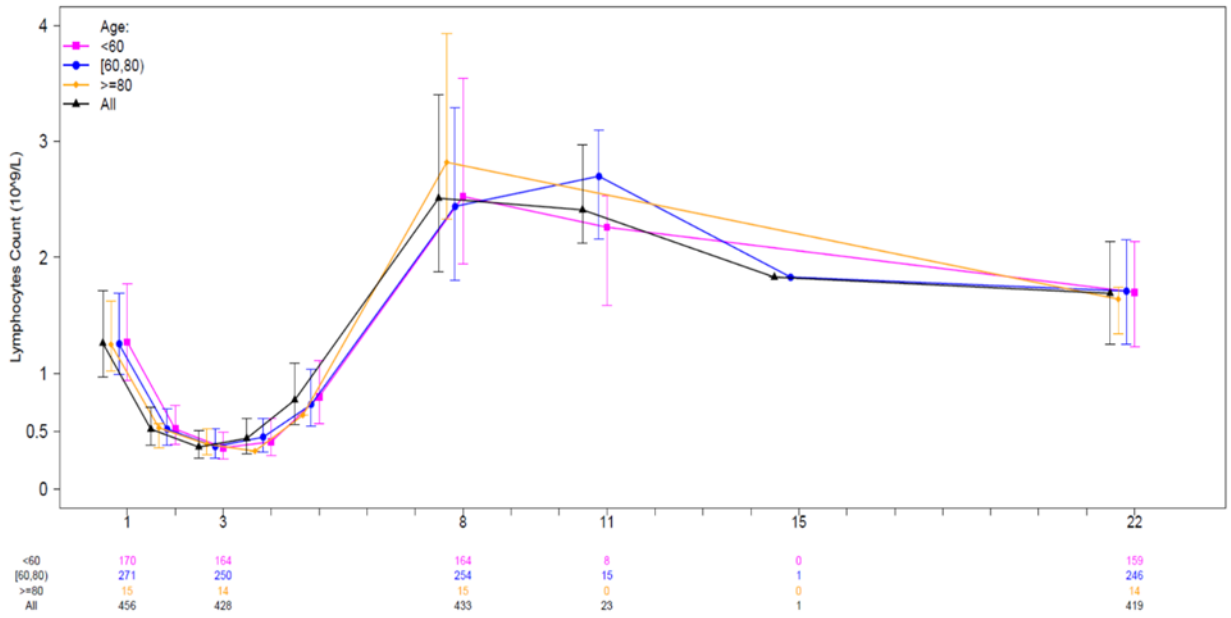
Figure 5: Bempegaldesleukin Increases Counts (Top Row) and Proliferation (Ki-67+, Bottom Row) in $CD4^+$, $CD8^+$, and NK^+ Immune Cells



Abbreviation: NK = natural killer

Peripheral blood mononuclear cell samples were obtained from 22 patients before treatment on Day 1 and after treatment on Day 8 after administration of bempegaldesleukin at doses of 0.003 to 0.009 mg/kg.
Source: Bentebibel 2019

Figure 6: Bempegaldesleukin (0.006 mg/kg) Reliably Increases Total Lymphocyte Counts in Patients with Cancer Across Age Groups (n=456)



% Lymphocyte count in Cycle 1 from standard hematology shows bempegaldesleukin at 0.006 mg/kg + nivolumab (360 mg) administered q3w increases percentage of lymphocytes in all age groups (<60, [60-80), ≥80 years of age). The initial decrease in blood lymphocyte counts is due to lymphocyte activation and extravasation into tissues followed by systemic proliferation.

Source: Study 16-214-02 (PIVOT-02)

In light of its mechanism of action, bempegaldesleukin may provide therapeutic benefit in COVID-19

2.1.4 Clinical Experience with Bempegaldesleukin

2.1.4.1 Studies of Bempegaldesleukin Therapy

Bempegaldesleukin is currently being studied in multiple clinical trials, and > 600 patients with locally advanced or metastatic solid tumors have been treated with bempegaldesleukin to date (Appendix 5). The range of doses tested in these oncology trials has been 0.003 to 0.012 mg/kg, which is higher than the dose range planned for the current COVID-19 trial, 0.00075 to 0.003 mg/kg.

Nektar initiated the bempegaldesleukin oncology development program with Study 15-214-01 (EXCEL), a Phase 1/2, open-label, multicenter, dose-escalation and dose expansion study of bempegaldesleukin monotherapy in patients with locally advanced or metastatic solid tumor malignancies. The study provided information on single-agent bempegaldesleukin safety and tolerability, pharmacokinetic (PK), the recommended Phase 2 dose (RP2D) in immuno-oncology, as well as efficacy and pharmacodynamic and immunological changes in blood and

tumor samples. The study was closed after 28 patients were enrolled in the dose-escalation phase. This allowed the oncology development program for bempegaldesleukin to continue with other studies in which bempegaldesleukin is administered in combination with checkpoint inhibitors, including nivolumab.

The combination of bempegaldesleukin with the checkpoint inhibitor nivolumab was initially investigated in a Phase 1/2 "basket" study (Study 16-214-02 [PIVOT-02]). This is an ongoing trial that includes patients with melanoma, RCC, non-small cell cancer, urothelial carcinoma, triple negative breast cancer, and other solid tumors. Results from Study 16-214-02 informed the oncology development program for bempegaldesleukin in combination with nivolumab, which currently encompasses multiple Phase 2/3 registrational studies, including patients with first-line metastatic and adjuvant melanoma, first-line RCC, and patients with metastatic urothelial carcinoma who are ineligible for cisplatin treatment. To date, the largest safety data set in aggregate has been collected in Study 16-214-02.

Breakthrough therapy designation was granted on 29 July 2019 for bempegaldesleukin in combination with nivolumab for the treatment of patients with untreated unresectable or metastatic melanoma based on data from the melanoma cohort in Study 16-214-02 (see Appendix 4 for additional details).

Bempegaldesleukin is administered in combination with nivolumab in several other studies, including CA045-010/18-214-14; 18-214-10/CA045-012 (PIVOT-10); CA045-001/17-214-08; 17-214-09/CA045002 (PIVOT-09).

In other studies, bempegaldesleukin is administered in combination with the checkpoint inhibitor pembrolizumab (Study 16-214-05 [PROPEL]) and the novel pegylated toll-like receptor 7/8 agonist NKTR-262 (Study 17-262-01 [REVEAL]). Bempegaldesleukin is also being studied in combination with avelumab, a human immunoglobulin (Ig)G1 monoclonal antibody directed against programmed cell death ligand 1 (PD-L1), with or without 1) talazoparib, a potent, orally bioavailable poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, and 2) enzalutamide, an androgen receptor inhibitor (Study B9991040). In addition, a study is underway in which bempegaldesleukin is administered in combination with the VB10.NEO vaccine, though no patients have as yet received the combination (Study VB N-01).

2.1.4.2 Safety Overview of Bempegaldesleukin

2.1.4.2.1 Study 15-214-01 (EXCEL) Bempegaldesleukin Monotherapy

The first in human trial with bempegaldesleukin was the monotherapy study EXCEL (Study 15-214-01 [NCT02869295]; 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 first part of the study was a dose escalation phase, designed to evaluate the safety and tolerability, and define the MTD or RP2D of bempegaldesleukin in patients with advanced cancers. The starting dose was 0.003 mg/kg and advanced to a maximum of 0.012 mg/kg. While the higher doses were relevant to explore the anti-cancer properties of the

compound, they are not relevant to the efficacy endpoint in this study nor is the safety profile of the higher doses representative of the level of risk anticipated for the lower doses used in this study.

In the monotherapy study, 28 patients received bempegaldesleukin and there were no National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 treatment-related adverse events (AEs) or deaths. At the highest dose tested, 0.012 mg/kg (or 16-fold the starting dose of this Phase 1b), one patient experienced two DLTs including Grade 3 hypotension and grade 3 syncope. The patient's AEs resolved within 24 hours following intravenous (IV) fluid treatment and one dose of tocilizumab. The patient continued to receive additional treatment with bempegaldesleukin at 0.006 mg/kg and the subsequent doses were well tolerated. Bempegaldesleukin at a dose of 0.009 mg/kg administered once every 3 weeks (q3w) was deemed the MTD by pre-defined dose-limiting toxicity criteria.

The most common treatment-emergent AEs (TEAEs) across the dose levels that were considered by the Investigator to be related to bempegaldesleukin were fatigue (71.4%), flu-like symptoms (67.9%), pruritus (64.3%), hypotension (57.1%), rash (50.0%), decreased appetite (46.4%), and arthralgia or cough (each 32.1%). Such treatment-related TEAEs as flu-like symptoms, rash, and pruritus were generally mild or moderate in severity, predictable, manageable, and short-lived. These AEs generally occurred approximately 3 to 4 days post-dose, and resolved spontaneously or were mitigated by nonprescription oral or topical treatments. The AEs corresponded to the pharmacokinetics of the active metabolites of bempegaldesleukin, which peaked at approximately 30 hours after dosing. The flu-like symptoms were managed with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and the cases of rash/pruritus were either self-limiting or treated with antihistamines.

Hypotension can be effectively mitigated by prophylaxis and hydration guidelines, which were introduced during Study 16-214-02 (PIVOT-02) and are now included in all studies of bempegaldesleukin (see Section 5.5.4).

The lowest bempegaldesleukin dose administered to date, 0.003 mg/kg, was utilized as monotherapy in Study 15-214-01 as part of the dose escalation process and represents the highest dose that could be administered in the current study (Study 20-214-34). Among the four patients treated at that dose there were no Grade 3 or higher instances of hypotension or any occurrence of cytokine release syndrome (see Table 4).

Table 4: Treatment-emergent Related Adverse Events by Severity Grade Following Bempegaldesleukin 0.003 mg/kg Administration (Study 15-214-01 [EXCEL])

Preferred Term	Bempegaldesleukin 0.003 mg/kg (q3w) (N=4)			
	All Cycles		Cycle 1 Only	
	Grade 1-2 n (%)	Grade 3-5 n (%)	Grade 1-2 n (%)	Grade 3-5 n (%)
Patients with ≥ 1 treatment-related TEAE	4 (100.0)	0	4 (100.0)	0
Flu-like symptoms[a]	2 (50)	0	1 (25)	0
Headache	2 (50)	0	1 (25)	0
Hypotension	2 (50)	0	2 (50)	0
Pruritus	2 (50)	0	2 (50)	0
Rash[b]	2 (50)	0	2 (50)	0
Dizziness	1 (25)	0	1 (25)	0
Abdominal pain	1 (25)	0	0	0
Chest discomfort	1 (25)	0	1 (25)	0
Conjunctivitis	1 (25)	0	1 (25)	0
Constipation	1 (25)	0	0	0
Depression	1 (25)	0	1 (25)	0
Dizziness	1 (25)	0	1 (25)	0
Dry skin	1 (25)	0	0	0
Dyspnea	1 (25)	0	0	0
Hypothyroidism	1 (25)	0	0	0
Muscular weakness	1 (25)	0	1 (25)	0
Nasal congestion	1 (25)	0	0	0
Nausea	1 (25)	0	0	0
Orthostatic hypotension	1 (25)	0	1 (25)	0
Pancreatitis	1 (25)	0	0	0
Rhinitis	1 (25)	0	0	0

Abbreviation: TEAE = treatment-emergent adverse event

a. Flu-like symptoms include the following preferred terms: “influenza-like illness”, “influenza”, “pyrexia”, “chills”

b. Rash includes the following preferred terms: “erythema”, “rash”, “rash erythematous”, “rash maculo-papular”, “rash papular”, “rash pruritic”, “rash pustular”, “rash vesicular”, “rash generalized”, “rash macular”

Patients reporting more than one AE within the same preferred term are counted once at the highest severity reported

Data cut off: 29 March 2018.
Source: t15.10teae_rel_post_v4, t15.12teae_rel_post_c1

2.1.4.2.2 Study 16-214-02 (PIVOT-02) Bempegaldesleukin and Nivolumab Combination Therapy

The PIVOT-02 trial (NCT02983045) is an ongoing Phase 1/2 open-label, multicenter, dose escalation, and dose expansion study of bempegaldesleukin in combination with nivolumab and other anti-cancer therapies in patients with locally advanced or metastatic solid tumors. Part 1 of the study was a dose escalation phase that initially evaluated bempegaldesleukin monotherapy in 22 patients at doses ranging from 0.003 mg/kg to 0.012 mg/kg.

Among the three patients treated with 0.003 mg/kg of bempegaldesleukin monotherapy in Study 16-214-02, there were no Grade 3 or higher instances of hypotension or any occurrence of cytokine release syndrome (Table 5).

Table 5: Treatment-emergent Related Adverse Events by Severity Grade Following Bempegaldesleukin 0.003 mg/kg Administration (Study 16-214-02 [PIVOT-02])

Preferred Term	Bempegaldesleukin 0.003 mg/kg (q3w) (N=3)			
	All Cycles		Cycle 1 Only	
	Grade 1-2 n (%)	Grade 3-5 n (%)	Grade 1-2 n (%)	Grade 3-5 n (%)
Patients with ≥ 1 treatment-related TEAE	3 (100.0)	0	3 (100.0)	0
Chills	3 (100.0)	0	2 (66.7)	0
Nasal congestion	2 (66.7)	0	0	0
Pruritus	2 (66.7)	0	1 (33.3)	0
Pyrexia	2 (66.7)	0	2 (66.7)	0
Rash[a]	2 (66.7)	0	1 (33.3)	0
Abdominal pain	1 (33.3)	0	0	0
Anal haemorrhage	1 (33.3)	0	0	0
Arthralgia	1 (33.3)	0	0	0
Constipation	1 (33.3)	0	0	0
Diarrhoea	1 (33.3)	0	0	0
Dry skin	1 (33.3)	0	1 (33.3)	0
Dyspepsia	1 (33.3)	0	0	0
Erythema	1 (33.3)	0	0	0
Eye pain	1 (33.3)	0	0	0
Face oedema	1 (33.3)	0	0	0
Facial paralysis	1 (33.3)	0	1 (33.3)	0
Fatigue	1 (33.3)	0	1 (33.3)	0
Flushing	1 (33.3)	0	1 (33.3)	0

Table 5: Treatment-emergent Related Adverse Events by Severity Grade Following Bempegaldesleukin 0.003 mg/kg Administration (Study 16-214-02 [PIVOT-02]) (Contd)

Preferred Term	Bempegaldesleukin 0.003 mg/kg (q3w) (N=3)			
	All Cycles		Cycle 1 Only	
	Grade 1-2 n (%)	Grade 3-5 n (%)	Grade 1-2 n (%)	Grade 3-5 n (%)
Headache	1 (33.3)	0	1 (33.3)	0
Hypotension	1 (33.3)	0	1 (33.3)	0
Lacrimation increased	1 (33.3)	0	0	0
Malaise	1 (33.3)	0	0	0
Oedema peripheral	1 (33.3)	0	0	0
Periorbital oedema	1 (33.3)	0	0	0
Pneumonia	1 (33.3)	0	0	0
Rash maculpapular	1 (33.3)	0	1 (33.3)	0

Abbreviation: q3w = every 3 weeks; TEAE = treatment-emergent adverse event

a Rash includes the following preferred terms: “erythema”, “rash”, “rash erythematous”, “rash maculo-papular”, “rash papular”, “rash pruritic”, “rash pustular”, “rash vesicular”, “rash generalized”, “rash macular”

Patients reporting more than one AE within the same preferred term are counted once at the highest severity reported.

Data cut off: 28 October 2019.

Source: Source: t14.9.2taebypt03_tr, t14.9.4taebypt03_g3tr, t14.9.6teabypt03_c1tr, t14.9.8teabypt03_c1g3tr

Information concerning the safety profile of higher doses of bempegaldesleukin used in the PIVOT-02 trial is available in the bempegaldesleukin Investigator’s Brochure.

2.1.4.2.3 Risk Period for Bempegaldesleukin Active Compounds

Bempegaldesleukin is a prodrug. The periods when AEs associated with bempegaldesleukin are most likely to appear are 1) during or shortly after completion of the IV infusion and 2) approximately 2-4 days following the infusion. Reactions during or after the infusion period typically manifest as transient flushing, chills, itching, rash, and flu-like symptoms. The principal period of risk is when the prodrug releases the active moieties. These active forms gradually increase after dosing and peak between 24 and 48 hours post-dose.

2.1.4.2.4 Cardiac Safety

Nektar conducted a comprehensive analysis of the cardiovascular safety of bempegaldesleukin and potential risk of QT prolongation. Nonclinical cardiovascular safety of bempegaldesleukin was evaluated in cynomolgus monkeys with IV administration. Electrocardiographic (ECG) changes were monitored following bempegaldesleukin administration throughout the clinical

development program. PK/ECG data from Studies 15-214-01 (bempegaldesleukin monotherapy) and 16-214-02 (bempegaldesleukin in combination with nivolumab) have served to characterize the drug effect on the corrected QT interval (QTc) interval at the proposed therapeutic dose for cancer 0.006 mg/kg every 3 weeks. By comparison, the starting dose of bempegaldesleukin in this Phase 1b is a single dose of 0.00075 mg/kg or one-eighth the proposed therapeutic dose in cancer patients. Dose selection for the study is discussed further in Section 2.2.4.

Exposure-response analyses of the QTc were conducted using ECG and plasma concentration data from Studies 15-214-01 and 16-214-02 (dose escalation part) in accordance with the FDA Guidance for Industry. A review of the nonclinical and clinical data indicates that bempegaldesleukin has a low risk for cardiac events.

Nonclinical safety pharmacology studies showed no effect on the QTc interval following a single dose of bempegaldesleukin in telemetry-instrumented monkeys or following 3-month repeat dosing at exposure > 3.5-fold higher than that at the dose of 0.006 mg/kg/dose that is used in ongoing trials in late-stage cancer patients.

The safety review of clinical data was conducted in a total of 471 cancer patients treated with either bempegaldesleukin monotherapy (Study 15-214-01), bempegaldesleukin in combination with nivolumab (Study 16-214-02) or bempegaldesleukin in combination with pembrolizumab or atezolizumab (Study 16-214-05). Based on the aggregate analysis on the retrieved AE cases from bempegaldesleukin studies, no signal indicating a causal relationship between bempegaldesleukin administration and QT prolongation or its cardiac complications (torsarde de pointes, ventricular tachycardia or sudden cardiac death) has been identified.

An increase in heart rate related to the hypotensive effect was seen. PK/PD simulated results for 2000 cancer patients receiving 0.006 mg/kg bempegaldesleukin showed a median baseline heart rate of 71 beats per minute (bpm) and a median peak increase of 15 bpm, which occurred at 2.6 days postdose. The magnitude of the peak was dose-related: following simulated doses of 0.003 and 0.009 mg/kg, the median peak increases were 11 and 18 bpm, respectively. While heart rate increases associated with bempegaldesleukin were well tolerated by the patients in Studies 15-214-01 and 16-214-02, similar heart rate increases could be clinically impactful in vulnerable patient populations. Hence, patients with decompensated congestive heart failure or critical coronary stenosis are excluded from bempegaldesleukin protocols, including Study 20-214-34.

QTc prolongation potential for bempegaldesleukin was evaluated after administration of bempegaldesleukin monotherapy (n=28 patients) and also after administration of bempegaldesleukin and nivolumab (n=38 patients). Bempegaldesleukin doses in both studies exceeded the recommended phase 2 dose of 0.006 mg/kg in late-stage cancer patients. Exposure-response analyses evaluated plasma concentrations of the active pegylated IL-2 conjugates formed after administration of bempegaldesleukin (NKTR-214-AC). Assessment of plasma concentration-QTc relationships did not show a correlation for QTc prolongation. Due to the increase in heart rate after bempegaldesleukin administration, several heart rate correction

methods in addition to the prespecified Fridericia method were used. QTcRMA correction had the smallest QTc-RR slope for both studies. Both NKTR-214-AC concentration-dQTcRMA and NKTR-214-AC concentration-dQTcF mixed-effects model predicted a decrease in QTc with increasing NKTR-214-AC concentrations. The predicted decreases in the corrected QT interval (calculated with Fridericia's formula; QTcF) and in QTcRMA were 17.3 and 11.0 msec, respectively, at the geometric mean C_{max} of 32.7 ng/mL observed at the 0.009 mg/kg dose of bempegaldesleukin. Central tendency analysis of dQTc showed similar results.

In summary, bempegaldesleukin was associated with a dose-related increase in heart rate and concentration-depended decrease in QTc. As the heart rate increases could be clinically impactful in vulnerable populations, patients with decompensated congestive heart failure or critical coronary stenosis are excluded from Study 20-214-34.

2.1.4.2.5 Hypotension and Capillary Leak Syndrome

No patients in studies of bempegaldesleukin have experienced capillary leak syndrome.

Hypotension has been characterized as an identified risk of bempegaldesleukin. Instances of hypotension appear around 1-4 days following the infusion of bempegaldesleukin, coinciding with the peak plasma concentration of the active pegylated IL-2 conjugates formed after administration of bempegaldesleukin (NKTR-214-AC). Patients with bempegaldesleukin-induced hypotension are usually rapidly responsive to fluid administration.

Importantly, while AEs of hypotension occurred in 2 of the 4 patients who received monotherapy with 0.003 mg/kg bempegaldesleukin, the lowest dose administered to date, none were higher than Grade 2 severity. By comparison, the starting dose of bempegaldesleukin in the amended Study 20-214-34 is 0.00075 mg/kg, ie, one-fourth the dose at which Grade 1 or 2 hypotension was observed in 2 patients. Dose selection for this study is discussed further in Section 2.2.4.

A specific management guideline, including prophylactic fluid administration, was implemented in ongoing bempegaldesleukin studies, which has successfully mitigated the risk of hypotension (refer to Section 6.2 [Warnings and Precautions] of the bempegaldesleukin Investigator's Brochure).

2.1.4.2.6 Flu-like Symptoms and Rash

Across all studies with bempegaldesleukin, flu-like symptoms including fever, chills/rigors, and influenza-like illness, are the most common AEs. In general, these symptoms are mild, transient, and consistent with the appearance of active pegylated IL-2 moieties following administration of the bempegaldesleukin prodrug. These AEs occur within a predictable time frame, approximately 1 to 4 days post-dose, and resolved spontaneously or were mitigated by nonprescription oral or topical treatments. The flu-like symptoms, along with rash, are managed with NSAIDs, acetaminophen, and antihistamines. These are not anticipated to compromise or worsen the respiratory status of COVID-19 patients.

2.1.4.2.7 Cytokine Release Syndrome

While the safety, tolerability, and PK of bempegaldesleukin have been well described in patients with advanced cancers, particularly at 0.006 mg/kg q3w, the possibility cannot be excluded of toxicity and PK differences between cancer patients and patients with COVID-19. Consequently, the current trial is designed to evaluate bempegaldesleukin, under close monitoring, in a mild COVID-19 patient population. This dose-finding study will focus on the safety, tolerability, and PK profile of bempegaldesleukin at a starting dose of 0.00075 mg/kg, which is 8 times lower than the immuno-oncology dose of 0.006 mg/kg and 12 times lower than the monotherapy MTD of 0.009 mg/kg.

In the bempegaldesleukin Investigator's Brochure, Edition 8.0, cytokine release syndrome (CRS) has been reported in 5 of 605 (0.8%) cancer patients who received bempegaldesleukin as either monotherapy or in combination with other therapeutics. Among the 3 patients who received bempegaldesleukin monotherapy and experienced cytokine release syndrome, two received a dose of 0.009 mg/kg and one received a dose of 0.012 mg/kg. In the combination regimens, two cases of cytokine release syndrome were reported in patients who received bempegaldesleukin 0.006 mg/kg with nivolumab 360 mg.

All events of cytokine release syndrome for those patients on bempegaldesleukin monotherapy were reported as Grade 2 in severity. Both patients receiving bempegaldesleukin with nivolumab experienced Grade 3 severity cytokine release syndrome events.

Following the release of Edition 8.0 of the bempegaldesleukin Investigator's Brochure, a Grade 4 cytokine release syndrome event was reported in a patient from Study 17-262-01 after 1 cycle of treatment with 0.006 mg/kg bempegaldesleukin followed by 4 cycles of treatment with 0.003 mg/kg bempegaldesleukin, each combined with 1.92 mg of NKTR-262, an intratumorally administered toll-like receptor agonist.

In this study, the selection of less advanced COVID-19 patients represents a population with lower circulating cytokine levels than more advanced patients. Combined with the anticipated lack of clinically relevant IL-6 production associated with the proposed starting doses of bempegaldesleukin, such patients are expected to be at low risk for exacerbation of the cytokine milieu due to the study drug. At the highest planned dose in Study 20-214-34 (0.003 mg/kg), IL-6 concentrations were below the limit of quantification in approximately half of the plasma samples (additional details are provided in Section 2.2.4.3).

2.1.4.3 Summary of Safety

The currently available safety data demonstrate that bempegaldesleukin is a generally well-tolerated immuno-oncology agent when administered to late stage cancer patients as monotherapy and in combination with other immunotherapies and chemotherapy. Bempegaldesleukin has also been shown to be generally well-tolerated in cancer patients aged ≥ 60 years. The most common AEs include Grade 1 and 2 flu-like symptoms, including fever,

chills/rigors, and influenza-like illness, which occur within a predictable time frame, approximately 1 to 4 days post-dose, and typically resolve spontaneously or are mitigated by nonprescription oral or topical treatments. These, along with rash, are managed with NSAIDS, acetaminophen, and antihistamines.

Hypotension, a known AE associated with both IL-2 and engineered cytokines, has been characterized as an identified risk of bempegaldesleukin. Instances of hypotension coincide with the peak plasma concentration of the active pegylated IL-2 conjugates formed after administration of bempegaldesleukin (NKTR-214-AC). Hypotension can be mitigated using the hydration management guideline, which has successfully reduced the frequency and severity of instances of hypotension in ongoing bempegaldesleukin studies and patients with bempegaldesleukin-induced hypotension are usually rapidly responsive to fluid administration.

Given the encouraging clinical activity to increase lymphocytes and the manageable toxicity profile, the potential for direct benefit in patients warrants evaluation of bempegaldesleukin with standard of care for COVID-19.

2.2 Scientific Rationale for Study Design

This Phase 1b study is designed to identify the RP2D of bempegaldesleukin in patients with mild COVID-19 with the long-term aim to advance to future studies evaluating bempegaldesleukin in hospitalized patients with moderate COVID-19 who are lymphopenic and at greater risk for mortality.

2.2.1 Rationale for Placebo Control

To objectively assess the safety and disease measurement of bempegaldesleukin treatment for adults with mild COVID-19, this study will be randomized, double-blind, and placebo controlled.

All patients will also receive the standard of care treatment for mild COVID-19 determined by the Investigator or institution, which should follow the approved prescribing guidelines in the country.

2.2.2 Rationale for Endpoints

This study is the first evaluation of bempegaldesleukin in patients with mild COVID-19, therefore, a primary objective of the study is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of bempegaldesleukin.

Another primary objective of the study is to identify the recommended Phase 2 dose (RP2D) of bempegaldesleukin in patients with mild COVID-19.

The final primary objective of the study is to assess the effect of bempegaldesleukin on the time course and extent of changes in absolute lymphocyte counts, as decreased levels of lymphocytes

have been associated with a fatal outcome in COVID-19 (Tan 2020a), and in Wuhan, China, 40% to 70% of hospitalized patients for COVID-19 had lymphopenia (Zhou 2020; Huang 2020; Tian 2020 [preprint]; Wang 2020). Increased levels of activated CD4+ and CD8+ T lymphocytes are observed in recovering patients (Qin 2020) and recovery from COVID-19 is accompanied by maintenance of lymphocyte counts and robust T cell activation. In patients with late-stage cancer, many who have compromised immune systems, a single IV infusion of bempegaldesleukin reliably elevated total lymphocyte counts at least 2-fold within one week after treatment in the vast majority of patients, regardless of age. Comparable increases were also observed after multiple successive treatment cycles. Hence, evaluating changes in absolute lymphocyte counts in patients with mild COVID-19 may be useful to assess the potential therapeutic benefit of bempegaldesleukin to improve the recovery time from the disease, shorten hospital stays, prevent respiratory decline, and decrease mortality from the infection in patients with more moderate COVID-19.

2.2.3 Duration of Treatment for Study Drug (Bempegaldesleukin or Placebo)

Study drug administration will be limited to a single dose administration and monitoring in the hospital or in-patient facility will occur for a minimum of 8 days (ie, from Day 1 [day of dosing] to at least Day 8).

Patients will receive study drug in a hospital or in-patient facility setting.

2.2.4 Justification for Dose of Bempegaldesleukin

The starting bempegaldesleukin dose of 0.00075 mg/kg will be administered as a single IV infusion over 15 (± 5) minutes in an initial cohort of 10 patients (5 bempegaldesleukin plus standard of care [referred to in this document as bempegaldesleukin/SOC] and 5 placebo plus standard of care [referred to in this document as placebo/SOC]). The range of doses that may be tested, 0.00075 to 0.003 mg/kg, is supported by data demonstrating the potential to be pharmacologically active with a low likelihood of the toxicity observed in studies of bempegaldesleukin in patients with cancer. This range is specifically supported by extensive clinical safety data, toxicology data, and clinical pharmacology data for bempegaldesleukin as described in Sections 2.2.4.1, 2.2.4.2, and 2.2.4.3, respectively.

As an additional measure of caution, the first two patients randomized and treated (1 bempegaldesleukin/SOC and 1 placebo/SOC]) in each dose cohort will serve as sentinel patients. A Cohort Review Committee (CRC) will monitor the 2 sentinel patients for safety and tolerability for the first 72 hours after study drug administration before additional patients are dosed within the same cohort. If the CRC determines additional patients may be randomized, 2 patients will be randomized (1 with bempegaldesleukin/SOC and 1 with placebo/SOC), treated with study drug, and observed for 72 hours. For every 2 patients, the Medical Monitor will review the blinded safety and tolerability data for the first 72 hours after study drug administration to determine if the next 2 patients may be randomized. At the conclusion of each dose level cohort, the CRC will assess the accumulated, blinded safety and tolerability data, as

well as any available PK, pharmacodynamic, and disease measurement data, to assess the benefit/risk profile and determine if dose escalation or de-escalation of bempegaldesleukin at dose levels up to 0.003 mg/kg is warranted.

2.2.4.1 Summary of Clinical Safety Data

The clinical experience with bempegaldesleukin administered either as monotherapy or in combination with nivolumab in cancer patients has illustrated a predictable safety profile manifesting as either acute infusion-related symptoms or related to the early appearance of the active cytokines 24-48 hours post-dose. These treatment emergent AEs are typically mild to moderate in severity and transient in nature. Hypotension is the most clinically concerning, but can be mitigated by maintaining the hydration status of the patient and by appropriate exclusion criteria. The starting dose, 12-fold lower than the maximally tolerated dose, and the single dose administration utilized in this study, minimize exposure to bempegaldesleukin providing a safety margin and allowing careful consideration of the effects of dose escalation or de-escalation. Additionally, the enrollment of COVID-19 infected patients with mild disease avoids the potential risk of an untoward contribution to the cytokine milieu that complicates the course of more advanced patients.

2.2.4.2 Summary of Toxicology Data

Good Laboratory Practice toxicology studies evaluated the safety of bempegaldesleukin administered every 14 days to Sprague Dawley rats (0.006 to 0.3 mg/kg) and cynomolgus monkeys (0.006, 0.03, and 0.1 mg/kg) for 15 weeks followed by an 8-week recovery period. The no observed adverse effect levels (NOAELs) established in the 15-week studies were 0.1 mg/kg for the rat and 0.03 mg/kg for the monkey. The monkey was identified as the most sensitive species and the starting bempegaldesleukin dose of 0.00075 mg/kg in Study 20-214-34 is 1/40th of the monkey NOAEL of 0.03 mg/kg.

Hypotension is the most clinically significant adverse effect in patients, but similar effects were not observed in monkeys. In spite of this difference, monkeys appeared to have similar sensitivity to humans in responding to the immunostimulatory effects of bempegaldesleukin. Details are provided below.

Treatment with bempegaldesleukin in the 15-week monkey study resulted in a pharmacologically expected, dose-responsive immune stimulation characterized by a cyclic pattern of clinical observations and increases in absolute lymphocyte counts following each dose administration (Table 6). The clinical observations were of minimal severity at the lowest dose tested (0.006 mg/kg), increased with dose level, and were not tolerated at the highest dose tested (0.1 mg/kg).

Bempegaldesleukin-related target organs at the NOAEL dose (0.03 mg/kg) included the gastrointestinal (decreased food consumption, liquid feces), immune (increased lymphocytes; immune cell infiltration and lymphoid organ enlargement), and skin (dry skin, scabs, rash).

Effects in skin and gastrointestinal systems were also noted in clinical trials with bempegaldesleukin. The skin changes observed in the monkey were noted following the fourth dose and therefore, not relevant to the current protocol for COVID-19 since a single dose administration is planned.

At the terminal sacrifice after 15-weeks of dosing, bempegaldesleukin-related microscopic findings at 0.03 mg/kg included minimal to moderate mixed inflammatory cell infiltrates in multiple organs (liver, urinary bladder, heart, adrenal medulla, thyroid, and/or kidney, lung, esophagus, and/or tongue) and immune organ changes (thymus and spleen) consistent with an inflammatory response. All findings were minimal and partially recovered after an 8-week, dose-free period.

Importantly, results from the 15-week monkey study showed that immune stimulation decreased with dose. At the lowest dose of bempegaldesleukin evaluated in the 15-week study, 0.006 mg/kg, minimal inflammatory cell infiltrates were observed and involved fewer tissues (liver, kidney, bladder, heart, and adrenal gland). All findings fully recovered after an 8-week, dose-free period.

As shown in Table 6, the fold change in absolute lymphocyte count was similar in the monkeys (at 0.006 mg/kg) and humans (at 0.003 mg/kg) when plasma exposures are comparable. Therefore, exposure-response for immunological effects was similar in monkeys and humans. A comparable degree of immune stimulation is expected in humans and monkeys at doses that produce similar plasma exposures. Given this relationship, the degree of immune stimulation observed in monkeys at 0.006 mg/kg is expected to be similar to the degree of immune stimulation in humans at 0.003 mg/kg. Furthermore, the degree of immune stimulation in patients at the starting dose of 0.00075 mg/kg in Study 20-14-34 is expected to be lower than that observed in monkeys at 0.006 mg/kg. As 0.006 mg/kg had minimal immunologic effects in the 15-week monkey study, the exposure-response data indicate a low risk of hyperinflammatory responses in patients treated with 0.00075 mg/kg.

Table 6: Bempegaldesleukin Plasma Exposures and Increases Absolute Lymphocyte Counts in Monkeys and Patients with Cancer

Species	Dose (mg/kg)	C_{max} (ng/mL)[a]	AUC (ng h/mL)[a]	AUC Ratio: Monkey-to -Human Starting Dose[b]	ALC Maximum Fold Change[c]
Monkeys	0.1	233	9940	54	5.6
	0.03	73	3330	18	3.2
	0.006	15	794	4	2.1
Humans	0.009	43	2190	-	2.6
	0.006	31	1460	-	2.2
	0.003	16	732	-	1.8
	0.0015	8	366	-	1.5
	0.00075	4	184	-	1.3

Abbreviation: ALC=absolute lymphocyte count; AUC =area under the concentration-time curve

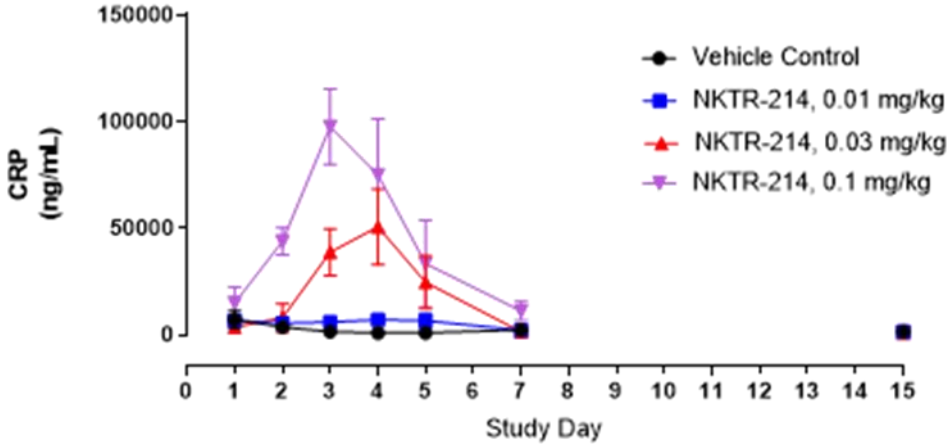
a. C_{max} and AUC are reported for NKTR-214-AC and values for monkeys were measured in Study LS-2017-033 (Day 1) and for humans were predicted (Table 7).

b. AUC Ratio: Monkey AUC at each dose level divided by human AUC at 0.00075 mg/kg

c. ALC Maximum values reported in monkeys (means; LS-2017-033) and in humans (medians) and are changes from baseline after the first dose of bempegaldesleukin.

Dose-related effects of bempegaldesleukin on C-reactive protein were well described in a single-dose toxicity study in monkey. As illustrated in Figure 7, transient increases in C-reactive protein were observed in the mid- and high-dose groups (0.03 and 0.1 mg/kg) during the first week after administration, with peak concentrations occurring on Days 3-4 (2-3 Days post-dose). In the low-dose group, 0.01 mg/kg, changes in C-reactive protein were minimal and only slightly higher than in the vehicle control. C-reactive protein was not evaluated in prior clinical studies of bempegaldesleukin. As plasma exposures with the 0.03 mg/kg dose in monkeys were more than 3-times higher than those predicted in patients over the range of doses in Study 20-214-34 (0.00075 to 0.003 mg/kg), bempegaldesleukin-related increases in C-reactive protein are not expected in this clinical study.

Figure 7: C-Reactive Protein Levels after Bempegaldesleukin Administration in Female Cynomolgus Monkeys (n=3)



Note: CRP = C-reactive protein; NKTR-214 = bempegaldesleukin
Source: A single dose bempegaldesleukin study in the cynomolgus monkey (LS-2012-002)

In summary, safety margins based on plasma exposures at the NOAEL dose in monkeys indicate an 18-fold area under the concentration-time curve (AUC) safety margin for the 0.00075 mg/kg starting dose in Study 20-214-34. In addition, the dose-relatedness of immune stimulation in the 15-week monkey study and calculated monkey-to-human exposure margins support that a low (0.00075 mg/kg), single dose of bempegaldesleukin is unlikely to result in a hyperinflammatory response in humans.

2.2.4.3 Summary of Clinical Pharmacokinetic/Pharmacodynamic Data

Prior clinical studies evaluated bempegaldesleukin in patients with advanced cancer at doses ranging from 0.003 to 0.012 mg/kg. A lower dose range was postulated to result in a favorable benefit risk profile in patients with mild COVID-19. Therefore, PK/PD modeling and dose-response evaluations were used to predict clinical effects at doses ≤ 0.003 mg/kg.

As bempegaldesleukin is being explored as a possible treatment strategy for increasing lymphocyte counts in patients with COVID-19, an endpoint of interest is the change in lymphocytes before and after treatment with bempegaldesleukin. This is quantified by measuring the fold change from baseline (ie, predose Day 1) absolute lymphocyte count to the maximal absolute lymphocyte count between Day 6 and Day 8. A PK/PD model was developed using data from Study 15-214-01 (EXCEL) in which bempegaldesleukin monotherapy was administered to cancer patients at doses of 0.003 mg/kg (N=4), 0.006 mg/kg (N=11), 0.009 mg/kg (N=5), and 0.012 mg/kg (N=1). The model predicted median absolute lymphocyte count changes of approximately 1.77-, 2.20-, and 2.6-fold for doses of 0.003, 0.006, and 0.009 mg/kg, respectively, which well described the observed changes within this dose range (Figure 4 and Table 3). The model also predicted median absolute lymphocyte count changes of

approximately1.32- and 1.49-fold for doses of 0.00075 and 0.0015 mg/kg, respectively. This suggests that the planned doses for Study 20-214-34, 0.00075, 0.0015, and 0.003 mg/kg are pharmacologically active.

Dose-response assessments were performed for 15 inflammatory cytokines to evaluate if bempegaldesleukin doses ≤ 0.003 mg/kg could cause hyperinflammation in patients with mild COVID-19. Data from cancer patients in Study 15-214-01 (EXCEL; bempegaldesleukin monotherapy) were evaluated for each of the cytokines shown in Table 7. Plasma concentrations were mostly below the limit of quantification for the following: granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon γ (IFN-γ), IL-3, IL-4, IL-7, and tumor necrosis factor β (TNF-β). Therefore, circulating levels of these 6 cytokines did not appear to be affected by bempegaldesleukin from 0.003 to 0.009 mg/kg. The results for the 9 remaining cytokines showed that increases in circulating cytokines generally occurred from day 3 to day 7 postdose, coinciding with the pharmacokinetic time course of bempegaldesleukin-related active cytokines (NKTR-214-AC). The percentage of plasma samples with measurable concentrations tended to increase with dose, suggesting dose-response relationships for IL-5, IL-6, IL-8, IL-10, IL-18, macrophage inflammatory protein 1α (MIP-1α), MIP-1β, monocyte chemotactic protein 1 (MCP-1), and TNF-α over the bempegaldesleukin dose range of 0.003 to 0.009 mg/kg. These dose-response relationships provide some assurance that any risks associated with bempegaldesleukin induced cytokines may be mitigated by using a low range of doses (0.00075 to 0.003 mg/kg).

A final analysis evaluated biomarkers of possible relevance to the risk of hyperinflammation, where the magnitude of response was evaluated at the highest planned dose in Study 20-214-34, 0.003 mg/kg. This analysis included the following biomarkers in plasma: monocytes, neutrophils, IL-6, and TNF-α. As illustrated in Figure 8, 0.003 mg/kg was not associated with meaningful changes in plasma levels of monocytes or neutrophils. As shown in Table 7, IL-6 concentrations were below the limit of quantification in approximately half of the plasma samples from patients treated at 0.003 mg/kg. Based on data from the remaining plasma samples from this cohort, levels of IL-6 increased no more than 2-fold in 3 of 4 patients treated with bempegaldesleukin at 0.003 mg/kg. In the fourth patient treated at 0.003 mg/kg, IL-6 levels showed a 4- to 6-fold increase on Days 2 to 3 postdose. Maximum IL-6 levels after one dose of 0.003 mg/kg of bempegaldesleukin ranged from < 6.8 to 41 ng/mL. It is difficult to interpret the significance of this transient increase in IL-6 because high statistical heterogeneity has been encountered comparing IL-6 levels between patients with complicated and non-complicated COVID-19 disease (Coomes 2020 [preprint]). Circulating TNF-α did not appear to be affected by 0.003 mg/kg bempegaldesleukin to a meaningful extent, as plasma concentrations of TNF-α were quantifiable in only 25% of the plasma samples from patients treated with 0.003 mg/kg (Table 7).

Taken together, the results of PK/PD modeling, dose-response assessments, and evaluation of biomarkers at the planned highest dose of 0.003 mg/kg show that bempegaldesleukin doses over

the range of 0.00075 to 0.003 mg/kg have the potential to be pharmacologically active with a low risk of inducing hyperinflammation in patients enrolled in Study 20-214-34.

Table 7: Cytokine Determinations in Plasma Samples from Patients Treated with Bempegaldesleukin (Study 15-214-01 [EXCEL])

			GM-CSF	IFN-γ	IL-3	IL-4	IL-5	IL-6	IL-7	IL-8	IL-10	IL-18	MIP-1α	MIP-1β	MCP-1	TNF-α	TNF-β
LLOQ (pg/mL)[a]			26	6.8	8.6	43	6	6.8	41	6.1	8.1	42	48	59	83	24	58
Dose[b]	*N*	*n*	*% of Tested Samples with Measurable Concentrations*														
0.003	4	40	0	0	0	0	33	45	0	70	35	75	13	75	75	25	0
0.006	15	143	0	1.4	0	0	42	59	0.7	69	48	100	29	90	97	22	0
0.009	6	54	0	5.6	0	5.6	43	70	3.7	59	50	100	39	96	98	30	0

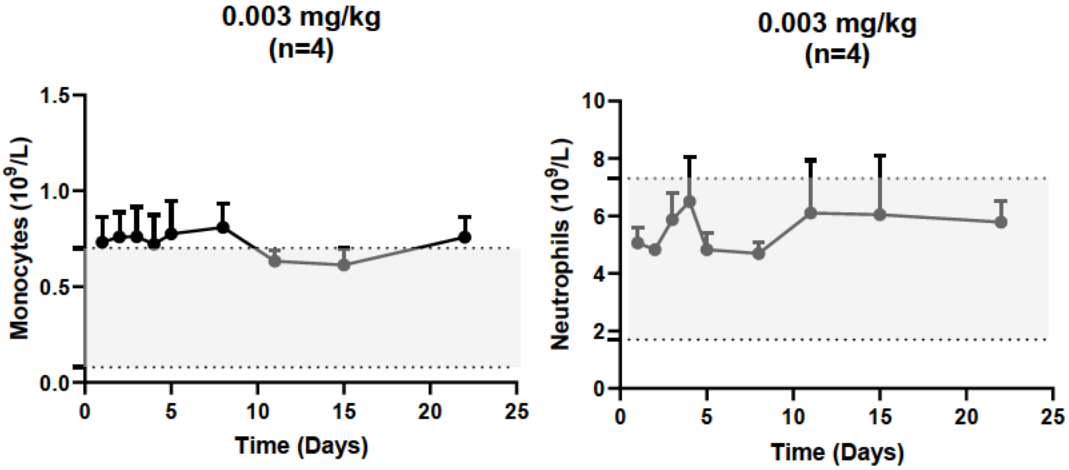
Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; LLOQ = lower limit of quantitation; MCP = monocyte chemotactic protein; MIP = macrophage inflammatory protein; N = the number of patients; n = the approximate number of samples evaluated in the multiplex cytokine assay; TNF = tumor necrosis factor

a. IL-3 concentrations are in ng/mL.

b. Doses are reported in units of mg/kg.

Source: Study 15-214-01 (EXCEL)

Figure 8: Monocyte and Neutrophil Profiles (Mean + SD) after Administration of 0.003 mg/kg Bempegaldesleukin (Study 15-214-01 [EXCEL])



Shaded areas indicated reference range for central laboratory.

Source: Study 15-214-01 (EXCEL)

2.3 Cohort Review Committee

In addition to routine safety monitoring and pharmacovigilance activities, a Cohort Review Committee (CRC, see Section 7.16) will be formed to review safety and tolerability data throughout the study. Specifically, the CRC will perform the following evaluations:

1. Monitor the blinded safety and tolerability data for the first 72 hours after study drug administration from the first two sentinel patients randomized (1 patient receiving bempegaldesleukin/SOC and 1 patient receiving placebo/SOC) and treated to determine if additional patients may be enrolled in the dose cohort. If the CRC determines additional patients may be randomized, 2 patients will be randomized (1 with bempegaldesleukin/SOC and 1 with placebo/SOC), treated with study drug, and observed for 72 hours. For every 2 patients, the Medical Monitor will review the blinded safety and tolerability data for the first 72 hours after study drug administration to determine if the next 2 patients may be randomized. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the Medical Monitor will request a review of the safety data by the CRC. It may be necessary for the CRC to review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.

2. Adjudicate reports of Grade 3 dose-limiting toxicities to determine if they meet the protocol-defined criteria for a DLT and demonstrate evidence indicating at least a possible relationship to study drug in patients confirmed to have received bempegaldesleukin. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.

3. At the conclusion of each dose level cohort, assess the accumulated, blinded safety and tolerability data, as well as any available PK, pharmacodynamic, and disease measurement data, to determine if dose escalation or de-escalation is warranted. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1) for the entire cohort to determine dose escalation, the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.

4. The CRC will also establish the RP2D.

All instances of patient unblinding will be performed in accordance with Nektar Therapeutics' internal procedures for unblinding and associated documentation.

The CRC will also meet on an ad hoc basis, if needed.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives are:

- To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of bempegaldesleukin/SOC compared with placebo/SOC in patients with mild COVID-19.
- To evaluate the safety and tolerability of bempegaldesleukin administered as single IV dose and to define the RP2D of bempegaldesleukin in patients with mild COVID-19.
- To assess the effect of bempegaldesleukin on the time course and extent of changes in absolute lymphocyte counts.

3.2 Secondary Objectives

The secondary objectives listed below involve comparison of bempegaldesleukin/SOC versus placebo/SOC in patients with mild COVID-19:

- To estimate the incidence of AEs.
- To evaluate the frequency of serious AEs (SAEs).
- To determine the percentage of patients who require supplemental oxygen.
- To evaluate clinical status based on the World Health Organization (WHO) Clinical Progression Scale. This will be determined once more information is obtained about the clinical meaning/interpretation. The scale is as follows:

Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: Moderate disease	Hospitalized, no oxygen therapy[a]	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; oxygen by non-invasive ventilation or high-flow	6
	Intubation and mechanical ventilation, $PaO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation, $PaO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation, $PaO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Death	10

Abbreviations: ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen; SpO_2 = oxygen saturation

a. If hospitalized for isolation only, record status as for ambulatory patient.

Source: WHO 2020

- To assess the immunologic effects in blood before and after study drug administration, including effects on cytokines, natural killer cells, T-cells, and other serum proteins and immune modulators.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Each patient will be entered into this study only if he/she meets all the following criteria:

1. Patient (or legally authorized representative) provides written, informed consent to participate in the study and follow the study procedures. The Investigator takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence.
2. Male or female patients, age 18 years or older on the day of signing the informed consent form (ICF).
3. Agrees to admission to an in-patient facility for monitoring from Days 1 to 8, inclusive.
4. Symptoms of mild illness with COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms) without shortness of breath, dyspnea, or clinical signs indicative of more serious COVID-19.
5. Confirmed COVID-19 determined by a positive, documented SARS-CoV-2 infection determined by a commercial or public health assay in any specimen within 4 days prior to the screening visit or during the 7-day screening period.
6. Respiratory rate < 20 breaths per minute.
7. Heart rate < 90 bpm.
8. Oxygen saturation by pulse oximetry > 93% on room air.
9. Body mass index < 35 kg/m^2.
10. Demonstrated adequate organ function, as defined below:
    a. Absolute neutrophil count (ANC) ≥ 1500/μL (≥ 1000/μL for patients with known or suspected diagnosis of benign ethnic neutropenia)
    b. Platelet count ≥ 100×10^3/μL
    c. Hemoglobin ≥ 12.0 g/dL
    d. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min, where eGFR is estimated by the Modification of Diet Renal Disease (MDRD) equation:
    $$eGFR\ (mL/min/1.73\ m^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$$
    e. Alanine transaminase (ALT) or aspartate transaminase (AST) or < 2 × upper limit of normal (ULN)
    f. Total bilirubin < 1.5× ULN

11. Reproductive Status

    a. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within the 7 days prior to enrollment.

    b. Women must not be breastfeeding.

    c. Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of study participation or 2 weeks after the last dose of study drug, whichever is longer. Women should use an adequate method(s) of contraception as indicated in Appendix 2.

    d. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 2) for the duration of study participation or 2 weeks after the last dose of study drug, whichever is longer. In addition, male patients must refrain from sperm donation during this time.

    e. Investigators shall counsel WOCBP, and male patients who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 2), which have a failure rate of < 1% when used consistently and correctly.

12. Patients must be able and willing to comply with the study procedures.

13. Agrees to not participate in another clinical trial for the treatment of COVID-19 while on study unless the patient's condition has worsened and is considered to be moderate, severe, or critical by the Investigator.

4.2 Exclusion Criteria

A patient will be excluded from this study if he/she meets any of the following criteria:

1. Shortness of breath, hypoxia (defined as the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] ≤ 300 mm Hg), or signs of serious lower airway disease.

2. C-reactive protein, lactate dehydrogenase (LDH), or IL-6 > 1.5 × ULN.

3. D-dimer or ferritin > 1.5 × ULN.

4. Imminently requiring, or currently on, mechanical ventilation or extracorporeal membrane oxygenation (ECMO) for respiratory support for COVID-19.

5. Systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg.

6. Patients with any evidence of acute respiratory distress syndrome (ARDS) or systemic inflammatory response syndrome (SIRS)/shock.

7. Known cardiovascular history including unstable or deteriorating cardiac disease including but not limited to the following:

    a. Unstable angina or myocardial infarction.

    b. Transient ischemic attack (TIA)/Cerebrovascular accident (CVA).

    c. Congestive heart failure (CHF) (any New York Heart Association [NYHA] Class).

    d. Uncontrolled clinically significant arrhythmias.

8. Patients with a history of autoimmune disease.

9. History of pulmonary embolism (PE), deep vein thrombosis (DVT), or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event.

10. Patients with central nervous system disease or evidence of central nervous system dysfunction.

11. Patients with any history of pulmonary disease, including cystic fibrosis.

12. Patients with a history of sickle cell disease.

13. Patients with a history of type 2 diabetes mellitus.

14. Patients with organ allografts.

15. Requirement for > 2 anti-hypertensive medications for management of hypertension (including diuretics). Patients with hypertension must be on a stable anti-hypertensive regimen for the 14 days prior to enrollment.
    Note: An antihypertensive medication that contains 2 drugs under one formulation is counted as 2 antihypertensive medications (eg, angiotensin-converting-enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).

16. Use of an investigational agent or an investigational device within 28 days of enrollment and throughout the course study, except if the patient's condition has worsened to moderate, severe, or critical per the Investigator.

17. Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive serum or urine pregnancy test.

18. History of allergy to bempegaldesleukin or its components, sodium citrate and trehalose dihydrate.

19. Patients on chronic immune-suppressive agents (use of 10 mg/day or less of prednisone or equivalent is allowed).

20. Has known hepatitis B virus (HBV) infection (eg, hepatitis B surface antigen [HbsAg] reactive) or hepatitis C virus (HCV) infection (eg, HCV ribonucleic acid [RNA] qualitative is detected).

21. Has known immunodeficiency or active human immunodeficiency virus (HIV-1 and HIV-2 antibodies).

22. Prolonged Fridericia's corrected QT interval (QTcF) > 500ms.

23. Unwilling to refrain from alcohol consumption from Day 1 of admission to the in-patient facility until discharge from the facility.

24. Patients with adrenal insufficiency.

25. Anticipated transfer to another hospital which is not a study site within the study duration.

26. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis).

5.0 INVESTIGATIONAL PLAN

5.1 Study Design

This study is a multicenter, Phase 1b, randomized, double-blind, placebo-controlled trial to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of bempegaldesleukin/SOC in adults with mild COVID-19, as well as to determine the RP2D of bempegaldesleukin.

5.2 Screening Period

Patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. After signing the ICF, patients will be evaluated for entry criteria during the up to 7-day Screening period based on assessments outlined in Section 1.2. Rescreening after screen failure may be allowed after discussion with the Medical Monitor.

5.2.1 Screening Failure

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities.

Patient re-screening: this study permits the re-screening of a patient who has discontinued the study as a pre-treatment screen failure (ie, patient has not been enrolled). If re-screened, the patient must be re-consented.

Retesting of laboratory parameters and/or other assessments included in the Schedule of Events (Section 1.2) within any single Screening period will be permitted if the Investigator deems the assessment does not accurately represent the patient's clinical status.

If laboratory parameters or other assessments were tested more than once, only the most current results obtained prior to enrollment will be used for assessment of eligibility. Results from earlier laboratory testing may not be substituted if repeat laboratory testing yields an exclusionary value.

5.3 Dose Finding

Dose finding is described in Table 8 and will follow the rules described in Section 5.3.1.

The first bempegaldesleukin dose to be studied (0.00075 mg/kg) was determined in consideration of a monotherapy trial with bempegaldesleukin in the oncology setting (ie, 0.003 mg/kg q3w; see Section 2.2.4.1) as well as non-clinical toxicology data (see Section 2.2.4.2) and clinical pharmacology and pharmacodynamic data (see Section 2.2.4.3, respectively). The starting dose is 12 times lower than the MTD for bempegaldesleukin

monotherapy established in patients with late-stage cancer. This dose has the potential to be pharmacologically active with a low risk of inducing hyperinflammation or toxicity in patients enrolled in Study 20-214-34 (Section 2.2.4).

Table 8: Dose Finding Scheme

Cohort	Bempegaldesleukin	
	Dose	**Schedule**
-1[a]	0.000375 mg/kg	single dose on Day 1
1	0.00075 mg/kg	single dose on Day 1
2[a]	0.0015 mg/kg	single dose on Day 1
3[a]	0.003 mg/kg	single dose on Day 1

a. Doses which may be chosen based on patient **response** to initial 0.00075 mg/kg dose.

In each dose cohort, the first two patients randomized and treated (1 with bempegaldesleukin/SOC and 1 with placebo/SOC) will serve as sentinel patients. Enrollment in each cohort will be staggered as presented in Figure 2 and Table 9. The Cohort Review Committee (CRC; see Section 7.16) will monitor blinded safety and tolerability data for the first 72 hours after study drug administration from the 2 sentinel patients before additional patients in that cohort are treated. If the CRC determines additional patients may be randomized, 2 patients will be randomized (1 with bempegaldesleukin/SOC and 1 with placebo/SOC), treated with study drug, and observed for 72 hours. For every 2 patients, the Medical Monitor will review the blinded safety and tolerability data from the first 72 hours after study drug administration to determine if the next 2 patients may be randomized (see Section 5.15). If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the Medical Monitor will request a review of the safety data by the CRC. After 10 patients have completed a 7-day observation period for DLT (see Section 5.3.2.1 for additional details), the CRC will determine whether dose escalation or de-escalation from the tested bempegaldesleukin dose level can proceed. The CRC will document this decision that will be based on blinded data using pre-defined criteria, including the proportion of patients who experience a DLT (see Section 5.3.2). Patients who drop out of the study for reasons other than a DLT, before the DLT evaluation period (Days 1 to 7) has elapsed, may be replaced.

Table 9: Staggered Dosing Procedures for Each Dose Cohort

Patient	Procedure
Patients 1 and 2	Randomize Patients 1 and 2.
	CRC reviews blinded safety and tolerability data for the first 72 hours after study drug administration to determine if Patients 3 and 4 can be randomized.
Patients 3 and 4	Randomize Patients 3 and 4 if CRC approves.
	Medical Monitor reviews blinded safety and tolerability data for the first 72 hours after study drug administration to determine if Patients 5 and 6 can be randomized.[a]
Patients 5 and 6	Randomize Patients 5 and 6 if Medical Monitor approves.
	Medical Monitor reviews blinded safety and tolerability data for the first 72 hours after study drug administration to determine if Patients 7 and 8 can be randomized.[a]
Patients 7 and 8	Randomize Patients 7 and 8 if Medical Monitor approves.
	Medical Monitor reviews blinded safety and tolerability data for the first 72 hours after study drug administration to determine if Patients 9 and 10 can be randomized.[a]
Patients 9 and 10	Randomize Patients 9 and 10 if Medical Monitor approves.
	After 10 patients receive study drug and a 7-day observation period has elapsed, CRC review to determine if dose escalation or de-escalation from the tested bempegaldesleukin dose level can proceed.

a. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the Medical Monitor will request a review of the safety data by the CRC.

The CRC will decide the following:

- Continued dosing of additional patients after the first 2 sentinel patients in a new cohort are treated and a 72-hour safety review period has elapsed. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.
- If reports of Grade 3 dose-limiting toxicities meet the protocol-defined criteria for a DLT and demonstrate evidence indicating at least a possible relationship to study drug in patients confirmed to have received bempegaldesleukin. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.
- Whether dose escalation or de-escalation from the tested bempegaldesleukin dose level can proceed after 10 patients are treated in a dose cohort and a 7-day observation period has elapsed. The CRC decision will be based on the accumulated, blinded safety and tolerability data, as well as any available pharmacokinetic, pharmacodynamic, and disease measurement data. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1) for the entire cohort to determine dose escalation, the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.

- The RP2D of bempegaldesleukin based on the totality of the blinded, safety, tolerability, pharmacokinetic, pharmacodynamic, and disease measurement data. The RP2D may be determined based on the MTD dose or a dose lower than MTD. The RP2D may also be determined based on the immunologic effects of the study drugs, which could include effects on lymphocyte counts, cytokines, natural killer cells, T-cells, and other serum proteins and immune modulators. If it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1) for the entire cohort to determine dose escalation, the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding.
- Whether dose levels other than those shown in Table 8 should be evaluated in consideration of the severity, duration, frequency of toxicities, pharmacokinetics, and/or pharmacodynamics observed at any dose.

5.3.1 Rules for Dose Finding

The DLT evaluation period will be a minimum of 1 week (7 days) (see Section 5.3.2.1).

Patients will be randomized (1:1 ratio) in groups of at least 10 patients (5 bempegaldesleukin/SOC and 5 placebo/SOC) in each dose cohort unless unacceptable toxicity is observed.

Unblinding patient treatment assignment, if required, for the purpose of dose-limiting toxicity (DLT) adjudication will be performed in accordance with Nektar Therapeutics internal procedures for unblinding and associated documentation.

The definition of a DLT is provided in Section 5.3.2.1. If no DLTs occur in a cohort of at least 5 patients who received bempegaldesleukin, a new cohort of 10 patients may be randomized and treated at the next higher dose level (Table 8). If only 1 of the 5 patients who received bempegaldesleukin in a dose cohort experiences a CRC-confirmed DLT, then the next cohort of 10 patients may be treated at the next higher dose level. If 2 or more patients who received bempegaldesleukin within a cohort experience CRC-confirmed DLTs, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 5 patients who received bempegaldesleukin has experienced a CRC-confirmed DLT). If 10 patients have already been enrolled into a cohort and additional patients have signed the ICF and are undergoing the screening process, they may be enrolled to the cohort with Sponsor approval; however, these patients are not required to be included in the dose escalation or de-escalation decision for that cohort.

Approximately 30 patients will be enrolled.

5.3.2 Dose-Limiting Toxicities (DLTs)

5.3.2.1 Determination of Dose-Limiting Toxicities (DLTs)

The DLT evaluation period will be a minimum of 1 week (7 days) because possible drug-related AEs are most likely to occur 1 to 5 days following bempegaldesleukin treatment based on the following:

- Previous experience with bempegaldesleukin in cancer patients including clinical safety data from 605 patients treated primarily with bempegaldesleukin at higher, oncology dose levels (most often, bempegaldesleukin 0.006 mg/kg) than will be used in this trial (see Section 2.2.4.1).
- The clinical half-life of bempegaldesleukin, which is approximately 20 hours (see Section 2.1.3.1).
- The rate of active species formation from the inactive bempegaldesleukin pro-drug (see Section 2.1.3).
- The chronic nonclinical toxicology studies (see Section 2.2.4.2).

DLTs will be assessed by the CRC during the DLT evaluation period. If DLTs are not observed, dose escalation will be permitted and enrollment of the next dosing cohort may begin. If DLTs are not observed, patients will continue to enroll until no more than 30 patients have been evaluable for safety. Grading of AEs is described in Section 7.3. Patients who drop out of the study for reasons other than a DLT, before the DLT evaluation period has elapsed, may be replaced.

5.3.2.1.1 DLTs Related to Study Drug

AEs related to study drug(s) that will be defined as a DLT include the following:

- Any Grade ≥ 3 drug-related AE.
- Any Grade ≥ 3 drug-related laboratory abnormality that is clinically significant per the Investigator.
- Respiratory compromise or other virus-related AE attributed to worsening COVID-19, such as severe hypoxia, cyanosis, or chest pain/pressure.

All AEs that meet DLT criteria must be recorded in the electronic data capture system within approximately 24 hours of awareness.

Each AE reported as related to study drug that meet any of the above definitions will be adjudicated by the CRC. If the event is confirmed to be at least possibly related to study drug, meets any of the above definitions, and is confirmed to have occurred in a patient treated with bempegaldesleukin, the event will be considered to be a DLT.

5.4 Study Stopping Criteria

The study will be promptly paused if any of the following are met:

- Death in any patient in which the cause of death is judged to be related to the study drug by the treating Investigator.
- The occurrence in any patient of a life-threatening SAE whose causal relationship to study drug is judged to be related by the treating Investigator.
- If at any dose tested, there are 2 occurrences of treatment-related dose-limiting toxicities defined in Section 5.3.2.1.1 observed in the first 5 or fewer patients dosed with bempegaldesleukin that are adjudicated by the CRC as meeting the criteria of Section 5.3.2.1.1 and are confirmed as related to study drug in patients actually treated with bempegaldesleukin.

If any of the above listed event(s) occur, patient accrual will be suspended pending further review by the CRC and prompt consultation with the US FDA and Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs).

5.5 Treatment Period

Patients who are not hospitalized on Day 1 will be admitted to an in-patient facility for monitoring.

Patients will receive a maximum of 1 dose of study drug (bempegaldesleukin or placebo) and will remain in the hospital or in-patient facility for monitoring until at least Day 8.

Study assessments for all patients will be performed as specified in Section 1.2. The following assessments should be collected for patients who are discharged prematurely from the in-patient facility:

- For patients who are discharged prior to Day 6: collect a sample between Days 6 to 10, inclusive, for the following:
  - Hematology and chemistry
  - Pregnancy test
  - PK assessments
  - Immunogenicity assessments
  - Respiratory specimens for detection of SARS-CoV-2 nucleic acid
  - SARS-CoV-2 serology
  - DNA/RNA sequencing
  - Immune cell profiling

- Cytokine assessments

  If the patient is unable to return to the clinic, the samples may be collected by research staff or designee at an alternate location.

- For patients who are prematurely discharged: site personnel should contact the patient by telephone each day until Day 8 for collection of AEs and concomitant medications.

If the timing of a protocol-mandated study procedure is skipped due to the patient's medical condition that precludes capturing the data or laboratory sample, the procedure or data should be captured on the nearest following feasible date.

5.5.1 Administration of Study Drug

Table 10 provides the timing of study drug administration.

Table 10: Selection and Timing of Dose

Study Treatment	Dose	Frequency of Administration	Route of Administration
Bempegaldesleukin (NKTR-214)	Starting dose: 0.00075 mg/kg[a]	Single dose on Day 1	IV over 15 (± 5) minutes
Placebo	Not applicable	Single dose on Day 1	IV over 15 (± 5) minutes
Standard of care	Determined by the Investigator and/or institutional guidelines.		

a. Other doses may be explored as described in Table 8.

5.5.2 Study Drug Dosing

Each patient's dose of study drug will be determined by the patient's dose cohort and weight in kilograms, which will be determined on the day of study drug dosing.

Patients should receive study drug at the starting dose determined by the patient's dose cohort on Day 1. Study agent(s) should be administered in an area with access to resuscitation equipment.

Study drug will be administered IV over 15 (± 5) minutes. The duration of infusion of study drug may be increased if necessary (eg, patient history of infusion reaction) (see Pharmacy Manual for details). The study drug infusion must be promptly followed by a flush with diluent to clear the IV line to ensure the full dose is administered. The total volume of study drug infusion should include the flush of diluent.

Patients should be carefully monitored for infusion reactions during study drug administration. If an acute infusion reaction is noted, patients should be managed according to the guidelines in Section 5.6.2.

Please refer to the Pharmacy Manual/current Investigator's Brochure for details regarding study drug reconstitution, preparation, storage, and administration.

5.5.3 Standard of Care Treatment Dosing

Patients will receive standard of care treatment determined by the Investigator or institution, which should follow the approved prescribing guidelines in the country. Study patients will not be permitted to receive other investigational treatments during the study period except if their condition has worsened to be considered "severe" or "critical" by the Investigator.

5.5.4 Monitoring, Vital Signs, and Hydration Guidelines

The study site must be equipped to monitor vital signs, respiratory status, cardiovascular status, among others, as well as being equipped to manage medical emergencies.

5.5.4.1 Vital Signs

Refer to Section 7.14 for vital sign measurements, which are to be monitored according to the Schedule of Events (Section 1.2).

5.5.4.2 Hydration Guidelines

Important safety information and hydration instructions are to be provided to patients. Details regarding IV hydration will be captured in the electronic data capture (EDC).

Adequate hydration mitigates the development of hypotension associated with bempegaldesleukin administration. Underlying reasons for decreased oral intake (eg, nausea) should be addressed and alternate hydration (eg, IV hydration) should be provided. The Investigator may modify these recommendations based on the needs of the individual patient.

Patients should receive IV fluid as tolerated on the day of study drug dosing and continue with oral hydration as tolerated for the subsequent 3 days. In the event patients cannot adhere to the oral hydration guidelines, IV hydration should be administered as clinically indicated. Patients should avoid activity that may contribute to dehydration.

As patients will be treated in an in-patient facility or a hospital, the aforementioned hydration guidelines may require adjustment. Therefore, IV hydration may be utilized for repletion of fluids on Days 2 to 4 post-dosing, rather than oral hydration. Hydration, whether IV or oral, should be titrated to the patient's degree of hypotension and should take into consideration the Investigator's assessment of the patient's clinical status. Per clinical judgment, IV fluids may be administered at any time during the study. The Investigator may decide to forego administering IV fluids to a patient or adjust the recommendation for self-oral hydration to a particular patient if this is deemed in the best interest of the patient (eg, evidence of fluid overload). Should fluid administration, whether oral or IV, be contraindicated, Investigators may utilize other methods of blood pressor support (eg, pressors) at their discretion.

If a patient is prematurely discharged from the in-patient facility before Day 4, site personnel must contact the patient (by telephone or clinic visit) once between Days 2 to 4, inclusive, to remind the patient of the oral hydration guidelines and to assess for any symptomatology and compliance with the hydration guidelines. Site personnel must document the hydration and the results of the discussion. Additionally, advise patients who are discharged from the in-patient facility before Day 8:

- To restrain from activities that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) from Days 1 to 8.
- If experiencing orthostatic symptoms, the patient should contact site personnel and consider increasing oral hydration.

5.6 Monitoring and Management Algorithms

5.6.1 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases can occur with bempegaldesleukin. The elevations in hepatic transaminases associated with bempegaldesleukin typically occur at the time of peak active cytokine concentration in the blood (Days 2-4), and are often accompanied by other AEs such as flu-like symptoms, rash, or pruritus. The transient elevations in hepatic transaminases are usually mild or moderate in severity, are not associated with increased total bilirubin, and resolve spontaneously without treatment.

5.6.2 Treatment of Study Drug-Related Infusion Reactions

Infusion reactions have been reported during infusions with bempegaldesleukin. If such a reaction were to occur with the study drug infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded as outlined below (consistent with CTCAE version 5.0 grading of infusion-related reaction); please also refer to Section 7.3.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

- For **Grade 1** symptoms (mild reaction; infusion interruption not indicated; intervention not indicated): Remain at the bedside and monitor the patient until recovery from symptoms.
- For **Grade ≥ 2** symptoms: Immediately discontinue study drug infusion and begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at the bedside and monitor the patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. Corticosteroid doses should be minimized (eg, ≤ 80 mg/day methylprednisolone) to avoid exacerbating impairment of immune function. Salbutamol may be given as 4 puffs (400 mcg) as the initial dose and increase by 2 puffs every 2 min up to 10 puffs if needed.

- For **Grade 3 or Grade 4** symptoms: immediately discontinue study drug infusion. Begin an IV infusion of normal saline and treat the patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Study drug will be permanently discontinued. The patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the patient until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

5.6.3 Management of Potential Cytokine Release Syndrome

Cytokine release syndrome (CRS) comprises a set of clinical sequelae arising from increased levels of circulating cytokines, including IL-6 and TNF-α. Potential clinical signs and symptoms include high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (eg, altered mental status, myoclonus, and seizures or seizure-like activity).

Cytokine release syndrome has been reported in 5 of 605 (0.8%) cancer patients who received bempegaldesleukin as either monotherapy or in combination with other therapeutics. There have been no CRS-related fatalities for any patient treated with bempegaldesleukin. Following the release of Edition 8.0 of the bempegaldesleukin Investigator's Brochure, a Grade 4 cytokine release syndrome event was reported in a patient from Study 17-262-01 after 1 cycle of treatment with 0.006 mg/kg bempegaldesleukin followed by 4 cycles of treatment with 0.003 mg/kg bempegaldesleukin, each combined with 1.92 mg of NKTR-262, an intratumorally administered toll-like receptor agonist (see Sections 2.1.4.2.7 and 2.2.4.3 for additional information).

In all cases of suspected CRS, contact the Medical Monitor as soon as feasible. Administration of low-dose corticosteroids (eg, 10 mg dexamethasone IV) and/or tocilizumab has demonstrated resolution of CRS symptoms and should be considered for first-line management of CRS in patients who are not at risk for life-threatening complications (Davila 2014).

5.7 Safety Follow-up

The Safety Follow-Up telephone call should occur 30 days (± 7 days) after discharge from the hospital or in-patient facility as described in Section 1.2. If a patient remains at the inpatient facility after Day 8, the Safety Follow-Up call should occur no later than 38 days (± 7 days) after Day 1, the day of study drug administration.

Collection of samples for immunogenicity, DNA/RNA sequencing, SARS-CoV-2 serology, immune cell profiling, and detection of SARS-CoV-2 nucleic acid should occur 30 days

(± 7 days) after discharge from the hospital or in-patient facility as described in Section 1.2. If a patient remains at the in-patient facility after Day 8, samples should be collected no later than 38 days (± 7 days) after Day 1, the day of study drug administration. If the patient is unable to return to the clinic, samples may be collected by research staff or designee at an alternate location.

The patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug as outlined in Sections 7.5 and 7.8. If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

For AE and SAE reporting periods, please refer to Sections 7.5 and 7.7.

5.8 Patient Discontinuation from Study

Reasons for patient discontinuation from the study include:

- Between Screening and Day 1, the patient's COVID-19 disease severity worsens to moderate, severe, or critical per the Investigator.
- Patient completes the study as follows:
  - Patient remains in the in-patient facility until Day 8 and completes the Safety Follow-Up 30 days after discharge from the in-patient facility.
  - Patient does not remain in the in-patient facility until Day 8, but completes the Safety Follow-Up 30 days after discharge from the in-patient facility.
- Patient decision to discontinue the study (follow-up data collection is allowed).
- Patient voluntarily withdraws consent from the study and all additional data collection.
- Death.
- Patient is lost to follow-up.
- Investigator's decision.

A patient may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or IRBs/ IECs.

Patients who have received study drug but discontinued early will be followed for safety when possible. Patients who receive study drug and are discharged from the hospital or in-patient facility will be monitored closely as outlined in Section 1.2.

5.8.1 Standard of Care Discontinuation Criteria

Investigators should follow the approved prescribing guidelines in the country, or institutional standard of care regarding dose discontinuation, dose modifications, and AE management for standard of care treatment.

5.9 End of Study

End of study is defined as no more than 6 months from enrollment of the last patient, or Sponsor decision.

5.10 Pharmacokinetic and Immunogenicity Measurements

Pharmacokinetic (PK) and immunogenicity (anti-drug antibodies [ADA]) assessment data will be collected from study patients at the sampling times indicated in Section 1.2.

All sampling times are relative to the start of the study drug administration.

Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Plasma PK samples will be analyzed for NKTR-214-RC (related cytokines; mixture of compounds containing IL-2 independent of PEG conjugation status) using a validated ligand binding assay.

Serum samples will be analyzed by multi-tiered ADA testing as per the 2019 FDA guidance (FDA 2019) to determine whether they contain ADAs that can bind to and neutralize bempegaldesleukin in the presence of the expected serum concentration of bempegaldesleukin. Validated methods to detect anti-bempegaldesleukin and anti-IL-2 ADA will be used to analyze immunogenicity samples. These assays are highly sensitive, demonstrate good drug tolerance, and were validated as per the 2019 FDA guidance (FDA 2019). Samples will be first tested with screening electrochemiluminescence assays (ECLA). Putative positive samples for anti-bempegaldesleukin or anti-IL-2 ADA will then be analyzed in a competition ECLA to confirm positivity. Confirmed anti-bempegaldesleukin ADA positive samples will be tested further in a PEG immuno-competition assay to determine the antibody specificity of the reactivity to the PEG or non-PEG (IL-2, linker) moiety of bempegaldesleukin. Confirmed positive samples from anti-bempegaldesleukin and anti-IL-2 ADA assays will then be tested to obtain a titer. Samples confirmed to be positive for anti-bempegaldesleukin and anti-IL-2 ADA will also be tested for neutralizing activity for IL-2 using a validated cell-based assay. A risk-based approach to evaluate and mitigate immune responses to or adverse immunologically related responses associated with bempegaldesleukin that affect its safety and efficacy would be adopted as per the 2014 FDA guidance (FDA 2014).

Blood samples designated for assessments (eg, PK, immunogenicity, serology, immune profiling) from the same collection time point may be used interchangeably for analyses, if required (eg, insufficient volume for complete assessment).

For all PK and ADA blood samples, the date and actual time collected must be recorded. For patients 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.

5.11 Biomarkers

Section 1.2 provides the biomarker sampling schedule, which includes samples for assessment of absolute lymphocyte counts, immune cell profiling, including profiling of SARS-CoV-2 specific T cells, assessment of cytokines, SARS-CoV-2 serology, sequencing of RNA/DNA (including whole genome sequencing of germline DNA, T and B cell receptor sequencing, and HLA haplotyping), and detection of SARS-CoV-2 nucleic acid in upper respiratory specimens. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

5.12 Prior and Concomitant Medications

All medications (prescription and over the counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the patient from Screening through the Safety Follow-Up call will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (eg, venipuncture) or prophylaxis of an infusion-related reaction should also be included.

Details regarding IV hydration will be recorded in the EDC.

5.12.1 Prophylaxis and Management of Symptoms Related to Immediate Infusion-Related Reactions (including Flu-Like Symptoms and Hypersensitivity Events)

Prophylactic treatment with a nonsteroidal anti-inflammatory, antipyretic, and antihistamine medications for flu-like symptoms and hypersensitivity events (eg, rash and/or pruritis), respectively, is recommended prior to bempegaldesleukin infusion at the discretion of the Investigator.

For post-infusion, flu-like symptoms and hypersensitivity events, treatment with nonsteroidal anti-inflammatory, antipyretic, and antihistamine medications may continue at the Investigator's discretion to manage the patient's symptoms. Additional treatment measures may be administered based on local treatment standards and guidelines, see Section 5.6.2.

5.12.2 Permitted Concomitant Medications

5.12.2.1 COVID-19 Treatment

Patients are permitted to receive any agent to treat COVID-19 (eg, antivirals) except for investigational agents or investigational devices within 28 days of enrollment and throughout the course of the study, except if the patient's condition has worsened to moderate, severe, or critical per the Investigator (see Section 4.2).

5.12.2.2 Antihypertensive Medications

Consideration should be given to temporarily withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hypertrophy), to minimize the risk of hypotensive events following administration of bempegaldesleukin. However, the discovery that COVID-19 binds to the ACE-2 receptor to gain entrance into cells highlights the potential role of the renin-angiotensin system (RAS) in the infectious process. Abrupt withdrawal of RAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability. While other antihypertensive therapy may be temporarily suspended for bempegaldesleukin administration, until further data are available it may be in the best interest of the patient to continue ACE inhibitors and angiotensin II receptor blockers (ARB). Study patients who are on medications such as beta-blockers, alpha blockers, calcium channel blockers, and nitrates should be able to temporarily discontinue these drugs. If withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to study drug administration. Antihypertensive medications may be reinstituted at any time as clinically indicated (eg, based on blood pressure monitoring result) (refer to Section 5.5.4.2).

5.12.2.3 Other Supportive and Palliative Care

Supportive and palliative medications used to treat symptoms of COVID-19 are allowed per institutional guidelines. Vaccination with inactivated viruses is permitted consistent with the institutional guidelines. Allow appropriate time interval between the most recent study treatment

administration and the next date of study treatment. If the patient experiences side effects after the flu vaccine or another inactivated vaccine, please manage study treatment administration per protocol guideline.

5.12.3 Effect of Bempegaldesleukin on the PK of Concomitant Medications

At the dose levels proposed for patients with COVID-19, bempegaldesleukin is expected to cause mild increases in circulating cytokines, some of which are known to have the potential to decrease the activity of multiple enzymes (CYP enzymes, hepatic flavin monooxygenases, UDP-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases) and drug transporters, and the suppressive effects can be additive (Haas 2005; Zidek 2009). The increases in circulating cytokines generally occur from day 3 to day 7 postdose, coinciding with the pharmacokinetic time course of bempegaldesleukin-related active cytokines (NKTR-214-AC). Consequently, treatment with bempegaldesleukin may lead to decrease in clearance of drugs that are substrates of these Phase I and Phase II drug metabolizing enzymes, or drug transporters from days 3 to 7 postdose. Several of the symptomatic or off-label treatments for COVID-19 have the potential to be subject to drug interactions. The magnitude of potential drug-interactions with bempegaldesleukin is unknown. Doses of drugs with narrow therapeutic index, including but not limited to chloroquine, and hydroxychloroquine, should be withheld from days 3 to 7 after administration of bempegaldesleukin. No pharmacokinetic drug interactions are expected with immunomodulatory treatments, including tocilizumab, sarilumab, and anakinra. Tocilizumab has been co-administered with bempegaldesleukin in studies 15-214-01 (2/28 [7%]) and 16-214-02 (3/541 [0.55%] patients), and corticosteroids have been co-administered with bempegaldesleukin in studies 15 214-01 (13/28 [36%] patients) and 16-214-02 (233/541 [43%] patients without definitive evidence of drug interactions. Consistent with guidance for remdesivir, hepatic laboratory testing should be performed prior to starting remdesivir and daily while receiving remdesivir. Close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted between Days 3 and Days 7 after bempegaldesleukin. Dose, timing, and duration of treatment for co-administered drugs for symptomatic or off-label treatment of COVID-19 must be recorded.

5.13 Adverse Events

All AEs, either reported by the patient or observed by study staff, will be reported from the time of first study drug(s) administration until 30 days after the last dose of study drug as described in Section 7.2.

5.14 Blinding

The Investigator, the patients, and all study site and Nektar personnel involved in study activities other than those involved in dispensing the study drugs must remain blinded to each patient's treatment assignment.

In circumstances when knowledge about the study drug received is required to adequately manage serious side effects or AEs experienced by the patient, for expedited reporting of SAEs

to the regulatory authorities or evaluation of severe AEs per the stopping rules described in Section 5.6.2 it may be necessary to unblind a patient's treatment regimen before all outcome assessments have been performed. If the Investigator believes that the study blind needs to be broken for a patient, the Investigator must contact the Nektar Medical Monitor. Unblinding will follow Nektar Therapeutics' internal procedures for unblinding and associated documentation. If the blind is broken, details surrounding the breaking of the blind (eg, date, time, and reason) are to be recorded in the patient's study file.

Bempegaldesleukin will be supplied open label to the clinical site.

An unblinded pharmacist not involved in any other aspect of the study conduct will be designated to manage and account for bempegaldesleukin, and to prepare the bempegaldesleukin or placebo dosing solution for blinded administration to each patient. The pharmacist will ensure that all other study personnel and patients remain blinded to treatment assignment. Study drug accountability for each dose cohort will also be performed by an unblinded monitor not otherwise associated with the day to day operational conduct of the study.

In the course of DLT adjudication, if it is not possible to assess the protocol-defined DLT criteria (see Section 5.3.2.1.1), the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding. Additionally, after 10 patients in a dose cohort have completed a 7-day observation period, if it is not possible to assess the protocol-defined DLT criteria for the entire cohort (see Section 5.3.2.1.1), the CRC may review unblinded data in accordance with Nektar Therapeutics internal procedures for unblinding to characterize the safety profile of bempegaldesleukin relative to placebo treatment to determine if dose escalation or de-escalation is warranted.

Unblinding of patient treatment assignment will follow Nektar Therapeutics' internal procedures for unblinding and associated documentation.

5.15 Method of Assigning Patients to Treatment Groups

For each dose cohort, two sentinel patients who meet all screening and eligibility criteria will be assigned randomly in a 1:1 ratio on Day 1 to receive either bempegaldesleukin/SOC or placebo/SOC. Following CRC review of the blinded safety and tolerability data from the first 72 hours after study drug administration for the 2 sentinel patients, the CRC will determine whether additional patients who meet all screening and eligibility criteria will be randomized in a 1:1 ratio within the dose group. Study drug administration will be staggered by 72 hours for every 2 patients (1 bempegaldesleukin/SOC and 1 placebo/SOC) to allow for Medical Monitor review of the blinded safety and tolerability data before the next 2 patients are randomized. As stated in Section 5.3.1, patients who drop out of the study for reasons other than a DLT, before the DLT evaluation period (Days 1 to 7) has elapsed, may be replaced. Therefore, in each dose cohort, a maximum of 10 patients will complete the 7-day DLT evaluation period (ie, a total of 5 patients who receive bempegaldesleukin/SOC and 5 patients who receive placebo/SOC). Study

drug assignment will occur in a blinded fashion in accordance with a computer-generated randomization scheme prepared by Nektar or its designee.

Each patient will be assigned a unique patient number after signing the ICF. Patient numbers will be used on all patients' study information. Patient numbers will not be reassigned.

An Interactive Response Technology (IRT) will be employed to manage patient randomization.

Nektar will supply bempegaldesleukin from a central source. Choice of standard of care for an individual patient will depend on what drug products are available at each medical center and the Investigator's choice.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

Table 12 provides the study treatments that will be administered in this study.

Table 12: Study Treatments Administered

Product Description	Content	Packaging / Appearance	Storage Conditions (per label)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		

[redacted]

6.1 Bempegaldesleukin (NKTR-214)

Bempegaldesleukin is the International Nonproprietary Name (INN) for NKTR-214.

6.1.1 Drug Description and Formulation

[redacted]

6.1.2 Drug Packaging and Labeling

[redacted]

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.

6.1.3 Drug Reconstitution and Handling

[redacted]

Refer to the Pharmacy Manual for detailed drug handling and administration information.

6.1.4 Drug Storage

[redacted]

6.1.5 Drug Shipment

[redacted] Refer to the Pharmacy Manual for additional details for ordering drug supply.

6.2 Placebo: Preparation, Storage, and Packaging

An unblinded pharmacist will prepare the placebo for infusion according to the instructions in the Pharmacy Manual.

The placebo dosing solution will be obtained as commercially available 0.9% Sodium Chloride Solution for Injection (USP).

6.3 Standard of Care: Preparation, Storage, and Packaging

Refer to the appropriate labeling requirements for details.

6.4 Study Drug Accountability and Reconciliation

Bempegaldesleukin will be supplied to the Investigator by Nektar Therapeutics or its designee. Depending on local health authority guidelines and drug availability, the standard of care may be obtained through commercial supply, the site pharmacy, or through a central depository. Depending on source of supply per specific country requirements, the packaging and labeling may vary. Products will be labeled to meet local country requirements. Please refer to the Pharmacy Manual for detailed information.

Study drug supplies must be kept in an appropriate, secure, locked area and stored in accordance with the conditions specified on the labels. Depending on local health authority guidelines, IV fluids and associated supplies (IV administration sets, calibrated pumps) may be obtained through commercial supply, the site pharmacy, or through a central depository.

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.

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.
- Doses prepared, time prepared, doses dispensed.
- Doses and/or vials destroyed.

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

7.0 ASSESSMENT OF SAFETY

7.1 AE Definition and Assessment

An AE is defined as any untoward medical occurrence in a clinical investigation patient 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, vital sign, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator (eg, associated with signs and symptoms, require treatment, or require follow-up).

An AE does not include:

- Pre-existing diseases or conditions present or detected before start of study drug(s) administration that do not worsen or increase in severity or frequency after the administration of study drug(s).
- Overdose of either study drug(s) or concomitant medication without any signs or symptoms.

7.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded, including but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 30 days following the last dose of study drug(s).

An event occurring after the patient 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 2 circumstances, the event will be considered an AE and will be captured as such.

- 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, and it will be documented as being “unrelated” to study drug(s), as applicable.

- Example 2: An ankle sprain following an unexpected fall from a flight of stairs while at home, after the patient has provided informed consent, but before the first dose of study drug(s), is clearly unrelated to any protocol-mandated procedures and would therefore be captured as medical history.

7.3 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 patient/event outcome or action criteria. All AEs, except for cytokine release syndrome, will be assessed for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines. For cytokine release syndrome, the modified CTCAE CRS grading scale should be used to assess severity (see Appendix 3). 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 [eg, insomnia, mild headache]).
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [eg, fever requiring antipyretic medication]).
- Grade 3 = Severe (event results in significant symptoms that prevent 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.

7.4 Causality Relationship of AEs

The relationship of each AE to each study drug (bempegaldesleukin or placebo) as applicable will be evaluated by the Investigator using the following definitions:

- Not related: An AE that does not follow a reasonable temporal sequence from administration of study drug(s), and/or that can be reasonably explained by other factors such as the patient's medical history, preexisting medical condition, underlying disease, concurrent illness, or concomitant medications/therapies.
- Related: There is a reasonable possibility that the AE is caused by the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug(s) and the development of the AE, or follows a known pattern to the study drug(s). The AE cannot be reasonably explained by the known characteristics of the patient's clinical state or other concomitant therapies or interventions administered to the patient.

7.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs will be reported from the time of first study drug(s) administration until 30 days of last dose of study drug(s). For SAEs, additional reporting requirements also apply (see Section 7.7).

All ongoing AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until the Safety Follow-Up call, whichever is earlier. In case the AE has not completely resolved by the Safety Follow-Up call, the final outcome of these ongoing AEs that are not related to study drug will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable. Any ongoing AEs at the Safety Follow-up call that are considered related to study drug will be followed until the event is resolved (with or without sequelae) or deemed stable. Any new AEs occurring after the Safety Follow-Up call will not be captured unless related to a study drug.

For specific instructions on identifying and reporting SAEs, see Sections 7.6 and 7.7.

7.6 Serious AE Definition

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

- Results in death.
- Is life threatening, ie, in the opinion of the Investigator, the AE places the patient 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 patient's participation in a clinical study.
- 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 patient 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 events leading to death, regardless of causality, must be reported. An efficacy failure is not considered an SAE. "Life-threatening" means that the patient 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 patient 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.

7.7 Serious AE Reporting

Serious AEs occurring after the patient 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 patient's medical that occur after the first dose of drug and meet the SAE criteria will be recorded as SAEs.

All SAEs, regardless of causality, with an onset within 30 days after the last dose of study drug(s) will be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge of the event.

In addition, SAEs that are assessed by the Investigator as related to study drug(s) and occurring after the SAE reporting period will also be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge of the event.

SAEs must be reported to Nektar Therapeutics Drug Safety via email or Fax as listed at the beginning of this protocol. Nektar Therapeutics may transition to reporting of SAEs via EDC while the study is ongoing. If this occurs, all sites will receive documented instructions regarding how to enter SAEs into EDC. If the study were to transition to reporting of SAEs in EDC, sites would continue to submit SAEs via email or Safety Fax as a backup system should there be EDC system access issues.

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 immediately without undue delay, under no circumstances later than 24 hours following knowledge of the follow-up information. Any medication or other therapeutic measures used to treat the event will be recorded.

All SAEs will be followed as described in Section 7.8.

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

7.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved by the Safety Follow-Up call 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 (eg, patient or health care practitioner refuses to provide additional information; lost to follow-up after demonstration of due diligence with follow-up efforts).
- The patient dies or is lost to follow-up.

All ongoing SAEs will be followed until resolution or until the Safety Follow-Up call, whichever is earlier. In the case where an SAE has not completely resolved by the Safety Follow-Up call, the final outcome of these ongoing SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

7.9 Adverse Events of Special Interest

Cytokine release syndrome (CRS) is considered an "adverse event of special interest" (AESI) and should be assessed for seriousness using the standard seriousness definition. However, all CRS events are required to follow the process and timeline for SAE reporting (within 24 hours as described in Section 7.7) from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com. Grading criteria for CRS are provided in Appendix 3.

7.10 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.7 for reporting details). A potential DILI is defined as:

- Treatment-emergent ALT or AST > 3 times ULN.

AND

- Total bilirubin > 2 times ULN or clinical jaundice, without initial findings of cholestasis (eg, elevated serum alkaline phosphatase > 2 times ULN).

AND

- No other immediately apparent possible causes of elevated liver enzymes and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.11 Pregnancy Tests/Pregnancy

7.11.1 Pregnancy Tests

Serum or urine pregnancy tests will be performed on WOCBP according to the Schedule of Events (Section 1.2). Urine pregnancy tests should have a minimum sensitivity of 25 IU/L or equivalent units of HCG. A negative pregnancy test result must be obtained before the administration of the study drug(s) and on the day of hospital discharge.

A pregnancy test does not need to be performed on women who are postmenopausal (see Appendix 2) for at least 1 year or surgically sterile for at least 3 months before signing the ICF.

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately. Requirements for reporting a pregnancy are provided in Section 7.11.2.

If, for whatever reason, the pregnancy has ended, confirmed by a negative serum pregnancy test, treatment may be resumed at the discretion of the Investigator (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended) following approvals of the patient/IRB/EC, as applicable.

7.11.2 Pregnancy

7.11.2.1 Pregnancies in Female Patients

The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up reports of a female patient becoming pregnant during the course of the study. All reports should be submitted via the Pregnancy Notification Form. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient 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 7.7. Female patient(s) who become pregnant will be followed 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 patient becomes pregnant, administration of the study drug(s) must be discontinued immediately.

7.12 Clinical Laboratory Tests

Clinical laboratory tests will be conducted at both a local laboratory and central laboratory according to the Schedule of Events (Section 1.2). A list of the clinical laboratory analytes to be tested is provided in Appendix 1. Local lab samples should be collected according to the Schedule of Events and the local lab will perform the tests listed in Appendix 1A. Central lab samples should be collected according to the Schedule of Events and the central lab will perform

the tests listed in Appendix 1B. All blood samples collected for central lab processing will be collected and sent to the central laboratory on the day of collection unless otherwise instructed.

For enrollment, if the central laboratory tests are cancelled, lost, unavailable, or considered inadequate for analysis, the site may forward an identical set of local laboratory results for eligibility review (with central laboratory testing repeated prior to the first dose of study drug). If local laboratory results are determined to be acceptable during eligibility review, enrollment may proceed.

Clinical laboratory test data will be reviewed by the Investigator or Sub-Investigator. Additional clinical laboratory tests may be ordered at the Investigator's or Sub-Investigator's discretion.

The Investigator or Sub-Investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (ie, is associated with signs and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in Section 7.1.

7.13 Physical Examinations

Physical examinations should be conducted according to the Schedule of Events (Section 1.2). Full physical examinations should be conducted at screening, and prior to dosing (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 targeted, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms.

7.14 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Events (Section 1.2). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation, and temperature. It is preferred that the same arm be used for all blood pressure readings, if possible. Weight is to be reported at screening and on the day of dosing, height at screening visit only.

7.15 Electrocardiograms

All patients will have 12-lead electrocardiogram (ECG) done during Screening as specified in the Schedule of Events (Section 1.2). ECG data will be locally assessed. After enrollment, the frequency of ECGs may be increased if clinically indicated.

7.16 Cohort Review Committee

A Cohort Review Committee (CRC) consisting of representatives from the Sponsor's Clinical Development, Drug Safety, Biostatistics, and other functional representatives as needed, and at least one Principal Investigator will meet to review safety and tolerability data, review the safety profile in the first 72 hours after study drug administration in the sentinel patients at the

beginning of each cohort, adjudicate AEs reported as DLTs, make decisions about escalating or de-escalating the dose of bempegaldesleukin, and identify the RP2D.

8.0 ASSESSMENT OF DISEASE MEASUREMENT

8.1 Disease Measurement Assessments

Screening and follow-up assessments should be acquired as outlined in Section 1.2.

8.1.1 Measures of Clinical Support and Limitations

The following measures of clinical support will be assessed at the first assessment of a given study day as outlined in Section 1.2:

- Limitations of physical activity.
- Hospitalization status (yes versus no).
- Oxygen requirement by mask or nasal prongs.
- Oxygen by non-invasive ventilation or high-flow.
- Intubation and mechanical ventilation requirement.
- ECMO requirement.

8.1.2 WHO Clinical Progression Scale

Table 13 provides the WHO Clinical Progression Scale, an 11-point clinical status ordinal scale, which will be used to measure COVID-19 clinical status and resource use over the course of the study (WHO 2020). The scale is an assessment of the clinical status at the first assessment of a given study day.

Table 13: WHO Clinical Progression Scale

Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: Moderate disease	Hospitalized, no oxygen therapy[a]	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; oxygen by non-invasive ventilation or high-flow	6
	Intubation and mechanical ventilation, $PaO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation, $PaO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation, $PaO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Death	10

Abbreviations: ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen; SpO_2 = oxygen saturation

a. If hospitalized for isolation only, record status as for ambulatory patient.

Source: WHO 2020

8.2 Other Assessment: Pharmacodynamic Measurement

A complete blood count with differential will be obtained to measure absolute lymphocyte counts as outlined in Section 1.2.

9.0 STATISTICAL PLAN

9.1 General Considerations

In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients. Unless otherwise specified, data will be summarized by treatment arm.

All disease measurement endpoints will be analyzed using all the patients who are enrolled. All safety endpoints will be summarized using the Safety population.

A detailed description of analysis methods will be provided in the statistical analysis plan (SAP).

9.2 Determination of Sample Size

This Phase 1b study will assess the safety and tolerability of different doses of bempegaldesleukin. No formal sample size calculation is done. Around 10 patients per dose cohort with a 1:1 randomization ratio (5 bempegaldesleukin/SOC and 5 placebo/SOC) to bempegaldesleukin/SOC or placebo/SOC will be enrolled.

9.3 Analysis Sets

For the purpose of analysis, the following populations are defined:

Population	Description
Safety Population	All patients who receive at least 1 dose (or partial dose) of study drug.
Pharmacokinetic Population	All patients in the Safety Population who have evaluable concentration-time profiles that allow for computation of meaningful PK parameter values.

9.4 Demographics and Baseline Characteristics

A descriptive summary of demographics and key baseline characteristics will be provided. Details will be included in the SAP.

9.5 Safety Analyses

The safety analyses will be based on the Safety population. For patients who receive placebo, the safety data will be pooled. Treatment-emergent AEs (TEAEs) will be defined as AEs that occur on or after receiving the first dose of study drug. The frequency of TEAEs will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred terms and treatment. In addition, by patient listings will be provided for TEAEs and SAEs.

9.6 Disease Measurement Analyses

Disease measurement analyses will be based on the Safety population.

The percentage of patients who require supplemental oxygen will be summarized by treatment group. The mean change from baseline in the WHO Clinical Progression Scale will be summarized by treatment group; changes to the analysis of this endpoint may be made in the SAP prior to database lock and unblinding of patient treatment assignment once more information is obtained about the clinical meaning and interpretation of the WHO Clinical Progression Scale (see Table 13).

[redacted]

9.7.1 Pharmacodynamics

The fold change from baseline at each evaluation time and the maximum fold change of absolute lymphocyte counts will be summarized descriptively by treatment group and a data listing will be provided. Changes to these pharmacodynamic endpoints may be made in the SAP prior to database lock and unblinding of patient treatment assignment.

9.7.2 Pharmacokinetics

Pharmacokinetic parameters such as C_{max}, time to C_{max} (T_{max}), and AUC will be estimated from plasma concentration-time data where possible. Pharmacokinetic parameters will be tabulated and summarized with descriptive statistics. Pharmacokinetic data obtained in this study may also be combined with data from other studies in the clinical development for the purpose of population PK modeling. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of bempegaldesleukin.

10.0 STUDY OR STUDY SITE TERMINATION

The Sponsor has the right to suspend or terminate the study or part of the study at any time for any reason.

If an Investigator suspends or terminates their study site, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

Subject to Institutional or other restrictions imposed as a consequence of the COVID-19 pandemic, the Sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

11.1 Changes to the Protocol

The Investigator may not deviate from the protocol without express permission from the Medical Monitor or a formal protocol amendment having been established and approved by an appropriate IRB/IEC, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable. All protocol deviations and the reasons for such deviations are to be documented in the source documents and reported to the Sponsor.

11.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, International Council on Harmonisation (ICH) GCP, and local regulations, the clinical monitor will periodically inspect all electronic case report forms (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 patients in this study. The names and identities of all research patients 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 Application (IND) regulations and ICH E6 guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient'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 before initiation of the study.

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

Members of the Sponsor or designees may conduct monitoring and auditing activities of a clinical site at any time during or after completion of the study. The Investigator will be informed of such activities.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives, may also conduct an inspection or perform an audit of the study. The Investigator(s)/institution(s) will permit trial-related audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents and study records. If informed of such an inspection, the Investigator should notify the Sponsor immediately. The Investigator will ensure that the inspectors and auditors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files are available, if requested.

12.0 ETHICAL CONSIDERATIONS

This study will be conducted to be consistent with the principles that have their origin in Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the current ICH GCP guidelines (ICH E6), as well as with any applicable regulatory authority, federal, state, and/or local laws and regulations.

12.1 IRB/IEC Approval

Before enrollment of patients into the study, as required by FDA regulations (21 CFR § 56), ICH GCP, applicable regulatory authority requirements, and local regulations, the current protocol and ICF 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 before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. 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 requirements, and in compliance with FDA regulations, applicable regulatory authority requirements, and ICH GCPs.

The Investigator, the Sponsor, or designee shall notify the IRB or IEC of any SAEs, suspected unexpected serious adverse reactions (SUSARs), or any other information that may affect the safe use of the study drug(s) during the study, per the IRB or IEC local requirements, and in compliance with FDA regulations, country and local regulatory authority regulations, and ICH GCPs.

12.2 Written Informed Consent

Written documentation of informed consent must be obtained from each patient or (if permitted by the local health authority) a patient's legal representative before entering the study. Patients will be informed of the nature of the study, and the ICF must be presented to each patient in the language in which the patient is fluent.

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

Any pregnancy that occurs in a study patient should be reported to the Sponsor or designee. For the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient must sign an informed consent form for disclosure information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Some health agencies have permitted alternate methods of obtaining informed consent from COVID-19 patients. These methods are acceptable per this protocol if the method of obtaining and documented informed consent is written in advance by the site and agreed to by the IRB/IEC.

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Instruments and Source Documents

13.1.1 Study Records

During the study, the Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. The Investigator/institution should, at a minimum, maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

13.1.2 Data Collection Instruments

Data collection instruments (DCIs) (eg, eCRFs, electronic clinical outcomes assessments [eCOA], and/or 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.

13.2 Retention of Essential Documents

For sites in the US: 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 approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer.

For sites outside the US: Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution when these documents no longer need to be retained.

To avoid any possible 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.

13.3 Confidentiality

Patient confidentiality will be maintained per local legal and regulatory requirements and applicable US federal regulations and ICH GCP guidelines. To comply with GCP guidelines and requirements, patient 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 patient identifying information, as confidential as possible as required by law.

Study data given to, and used by, Nektar are protected by the use of a patient identification number. The assignment of unique patient identification number to each patient by Interactive Response Technology (IRT) system enables de-identification.

Demographic identifiers that will be collected as part of Study Data include year of birth, age, gender, race, and ethnicity. Exact date of birth and patient name/initials are not collected.

The study site is not to provide any personal data relating to the patient from Study Data that will be transferred to Nektar. Only the study site will be able to connect the patient identification number a patient’s personal data.

13.4 Security Measures

Sites will employ both technical and organizational measures (such as, but not limited to, controlling access to personal patient data to only those with a need to know such data, data encryption, data anonymization and pseudonymization, and so forth) to ensure patient and patient data privacy. Sites will adhere to a “privacy by design” and “privacy by default” approach in collecting, storing, and processing personal patient data.

In the event of a breach of the security measures used by the Site to ensure patient and patient data privacy, the Site will immediately notify the Sponsor.

14.0 PUBLICATION PLAN

All data are the property of the Sponsor. Any formal presentation or publication of data from this study will be considered for joint publication by the Sponsor personnel and Investigator(s).

Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement governing participation in the study. Study data shared by Nektar will not contain patient identifiable information.

The 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.

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APPENDIX 1: CLINICAL LABORATORY TESTS

Descriptions of the laboratory tests performed in this study and study drug dosing criteria are provided in the following appendices:

- Appendix 1A: Local Laboratory Tests Performed in this Study
- Appendix 1B: Central Laboratory Tests Performed in this Study

Appendix 1A: Local Laboratory Tests Performed in this Study

Local Clinical Laboratory Tests[a]		
Hematology	**Chemistry**	**Serology**
• Hemoglobin (Hgb) • Platelet count • Neutrophils • Lymphocytes	• AST (SGOT) • ALT (SGPT) • Creatinine for estimated glomerular filtration rate (eGFR) • Total bilirubin • Lactate dehydrogenase (LDH)	• Hepatitis B • Hepatitis C • Human immunodeficiency virus (HIV)
Coagulation	**Additional Labs**	
• Partial thromboplastin time (PTT) • Prothrombin time (PT) • D-dimer	• C-reactive protein • Ferritin • IL-6 • Pregnancy test	
Urinalysis		
• Specific gravity • pH • Glucose • Protein • Bilirubin • Ketones • Leukocyte esterase • Blood	For positive protein, white blood cell or blood, a microscopic examination including: • Red blood cells • White blood cells • Epithelial cells • Bacteria • Crystals • Casts	

a. See inclusion criteria in Section 4.1 and exclusion criteria in Section 4.2.

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Appendix 1B: Central Laboratory Tests Performed in this Study

Central Clinical Laboratory Tests	
Hematology	**Chemistry**
• Hemoglobin (Hgb) • Hematocrit (HCT) • Platelet count • White blood cell (WBC) count • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	• AST (SGOT) • ALT (SGPT) • Alkaline phosphatase (ALP) • Albumin • Creatinine • Calculated creatinine clearance • Calcium • Glucose (non-fasting) • Total protein (TP) • Total bilirubin • Sodium • Potassium • Chloride • CO_2 content or bicarbonate • Blood urea nitrogen (BUN) or serum urea • Lactate dehydrogenase (LDH) • Uric acid
Coagulation	**Additional Labs**[a]
• Partial thromboplastin time (PTT) • Prothrombin time (PT) • D-dimer	• Creatine kinase • Thyroid stimulating hormone (TSH) • Free thyroxine (T4) • Free or total triiodothyronine (T3) • Lipase • Amylase • FSH[b] • C-reactive protein • Ferritin • IL-6[c] • ABO Group and Rh(D) Type • SARS-CoV-2 serology • Detection of SARS-CoV-2 nucleic acid in respiratory specimens[d]

a. See Section 5.11 for additional biomarkers that will be collected and analyzed at a central lab.

b. Post-menopausal females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause (see Appendix 2).

c. Of the Additional Labs specified in this list, IL-6 is the only one that may be tested at Screening by the central laboratory.

d. SARS-CoV-2 nucleic acid will be measured using a RT-PCR assay (see Section 5.11).

APPENDIX 2: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTON

DEFINITIONS

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as during study participation or 2 weeks after the last dose of study drug, whichever is longer (Note: local laws and regulations may require use of alternative and/or additional contraception methods).

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly*.[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP patients who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1.2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP patients chooses to forego complete abstinence
NOTES: a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the investigational medical products and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. c. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception[a]
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

a. Local laws and regulations may require use of alternative and/or additional contraception methods.

CONTRACEPTION GUIDANCE FOR MALE PATIENTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male patients with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Male patients are required to use a condom for study duration and until end of relevant systemic exposure defined as during study participation or 2 weeks after the last dose of study drug, whichever is longer.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined during study participation or 2 weeks after the last dose of study drug, whichever is longer in the male patient.
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during study participation or 2 weeks after the last dose of study drug, whichever is longer.
- Refrain from donating sperm for the duration of study participation or 2 weeks after the last dose of study drug, whichever is longer.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information is provided in Section 7.11.2.

APPENDIX 3: GRADING CRITERIA FOR CYTOKINE RELEASE SYNDROME

Grade	Description of Symptoms
1 Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (eg, fever, nausea, fatigue, headache, myalgias, malaise)
2 Moderate	Require and respond to moderate intervention: • Oxygen requirement < 40%, OR • Hypotension responsive to fluids, OR • Grade 2 organ toxicity (by CTCAE version 5)
3 Severe	Require and respond to aggressive intervention: • Oxygen requirement ≥ 40%, OR • Hypotension requiring vasopressor support, OR • Grade 3 organ toxicity (by CTCAE version 5)
4 Life-threatening	Life-threatening • Requirement for ventilator support OR • Grade 4 organ toxicity (by CTCAE version 5)
5 Fatal	Death

Source: Grading criteria modified from Lee 2014.

APPENDIX 4: BREAKTHROUGH DESIGNATION STATUS: MELANOMA

Breakthrough therapy designation was granted on 29 July 2019 for bempegaldesleukin in combination with nivolumab for the treatment of patients with untreated unresectable or metastatic melanoma based on data from the melanoma cohort in Study 16-214-02 (PIVOT-02). More recent study results for the melanoma cohort with the data cut of 25 September 2019 (18.6 months median follow-up) are consistent regarding the benefit/risk previously reported for this cohort in the breakthrough therapy designation application (12.7 months median follow-up). A continued deepening of the response to treatment with bempegaldesleukin plus nivolumab has been observed in this cohort as the median duration of follow-up has increased.

The complete response rate of 34.2% (13/38) (95% CI 19.6%, 51.4%) based on the response evaluable population, or 31.7% (13/41) based on the intent-to-treat (ITT) population, at both 12.7 months and 18.6 months of median follow-up, suggested a synergistic effect when these two agents are combined. In particular, of the patients showing responses (n=20), 65% (13/20) achieved a complete response. Median duration of response to bempegaldesleukin plus nivolumab at 18.6 months of follow-up has not been reached, consistent with prior trials that show responses to immunotherapy are durable. In addition, the median progression-free survival has not been reached. As a comparison, with a median follow-up of approximately 1 year, the complete response rate for nivolumab was 8.9% and the median progression-free survival was 6.9 months (Robert 2015). It is noteworthy that median time to complete response for treatment with bempegaldesleukin plus nivolumab was only 7.9 months. The early achievement of the complete response rate of 34.2% and apparent durability with bempegaldesleukin plus nivolumab as first-line therapy in patients with locally advanced and metastatic melanoma appears to offer a substantial improvement over available therapies. These results stress the importance of the activation of the IL-2 receptor pathway as a fundamental component of human immunity and a continued role for IL-2 in cancer immunotherapy, and underscore the relevance of bempegaldesleukin in combination with checkpoint inhibitors.

APPENDIX 5: CLINICAL STUDIES OF BEMPEGALDESLEUKIN (NKTR-214)

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
Phase 1 Study					
CA045-010/ 18-214-14 1 site in Japan	A Phase 1 Study to Evaluate Safety and Tolerability of NKTR-214 (BMS-986321) Administered in Combination with Nivolumab (BMS-936558) in Advanced Malignant Tumors (Bristol Myers Squibb)	To assess the safety and tolerability of bempegaldesleukin in combination with nivolumab in participants with advanced malignant tumors	Patients aged ≥ 20 years with advanced (metastatic and/or unresectable) malignant solid tumor	Bempegaldesleukin 0.006 mg/kg q3w + nivolumab 360 mg q3w	6/3 Completed
Phase 1/2 Studies					
15-214-01 (EXCEL)[a] (Part 1) 1 site in US	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 (Nektar Therapeutics)	To evaluate: • safety and tolerability, and define the MTD, of bempegaldesleukin • efficacy of bempegaldesleukin by assessing the ORR at the MTD or the dose below the MTD	Patients with locally advanced or metastatic solid tumors	**Part 1 (dose escalation):** Bempegaldesleukin Dose (mg/kg) Schedule 0.003 q3w (n = 4) 0.006 q3w (n = 11) 0.006 q2w (n = 6) 0.009 q3w (n = 6) 0.012 q3w (n = 1)	50/28 Completed[a]

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
VB N-01	Open Labelled First Human Dose Phase 1/2a Study to Evaluate Safety, Feasibility, Efficacy of Multiple Dosing With Individualised VB10.NEO and Bempegaldesleukin (NKTR-214) Immunotherapy in Patients With Locally Advanced or Metastatic Melanoma, Non-small Cell Lung Cancer (NSCLC), Clear Renal Cell Carcinoma, Urothelial Cancer or Squamous Cell Carcinoma of Head and Neck, Who Did Not Reach Complete Responses With Current Standard of Care Immune Checkpoint Blockade. (Vaccibody)	• To assess the safety/tolerability of multiple doses of 3 mg VB10.NEO immunotherapy and of multiple doses of 3 mg VB10.NEO immunotherapy in combination with 0.006 mg/kg bempegaldesleukin (NKTR-214) • To determine the feasibility of VB10.NEO (overall process feasibility from biopsy, sequencing, neoepitope selection and vaccine manufacturing)	Patients with locally advanced or metastatic solid tumors	VB10.NEO, 3 mg VB10.NEO (DNA plasmid pUMVC4a -VB10.NEO; individualised VB10.NEO immunotherapy) with 3 vaccinations q3w during induction period, followed by maintenance period with vaccinations q4w for up to 1 year from first immunization (total of 14 vaccinations). Intramuscular administration Bempegaldesleukin 0.006 mg/kg administered intravenously starting from Week 11 (Visit 8A or at any dosing visit up to week 34 [visit 14]) and for up to week 50 (up to 11 doses). The first 2 doses will be q3w interval and following doses q4w.	50/4 Ongoing (As of 27 March 2020 no patients have received bempegaldesleukin)
B9991040	A Phase1b/2 Study to Evaluate Safety and Clinical Activity of Avelumab in Combination with Bempegaldesleukin (NKTR-214) with or without Talazoparib or Enzalutamide in Participants with Locally Advanced or Metastatic Solid Tumors (Pfizer)	• Phase 1b: • To assess the dose-limiting toxicity (DLT) rate of avelumab in combination with bempegaldesleukin (NKTR-214) (Combination A) and talazoparib (Combination B) or enzalutamide (Combination C) in order to determine the recommended Phase 2	Patients with locally advanced or metastatic squamous cell carcinoma of the head and neck Patients with metastatic castration-resistant	Combination A starting dose: 800 mg avelumab IV q2w + 0.006 mg/kg bempegaldesleukin IV q2w Combination B starting dose: 800 mg avelumab IV q2w + 0.003 or 0.006 mg/kg bempegaldesleukin IV q2w (depending on dose established in combination A) + talazoparib PO 1 mg once daily Combination C starting dose: 800 mg avelumab IV q2w + 0.003 or 0.006 mg/kg	160/2 (as of 27 March 2020)

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
		dose (RP2D) for the combinations. Phase 2: • Combination A: To assess ORR of avelumab in combination with bempegaldesleukin (NKTR-214) in participants with locally recurrent or metastatic SCCHN. • Combination B: To assess soft tissue ORR of avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib in participants with DDR defect positive mCRPC • Combination C: To assess the PSA response rate of avelumab in combination with bempegaldesleukin (NKTR-214) and enzalutamide in participants with mCRPC after progression on abiraterone	prostate cancer	bempegaldesleukin IV q2w (depending on dose established in combination A) + enzalutamide PO 160 mg once daily	

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
16-214-02 (PIVOT-02)[b] ~75 sites: Part 1: US Part 2: US, Canada, UK, France, Spain, Australia, and Hong Kong Part 3: US Part 4: US	A Phase 1/2, Open-label, Multicenter Study of the Combination of NKTR-214 and Nivolumab or the Combination of NKTR-214, Nivolumab, and Other Anti-Cancer Therapies in Patients with Select Locally Advanced or Metastatic Solid Tumor Malignancies[b] (Nektar Therapeutics)	• To evaluate the safety and tolerability, and define the MTD and/or RP2D of bempegaldesleukin in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies • To evaluate the efficacy of bempegaldesleukin in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies by assessing the ORR by RECIST v1.1 at the RP2D	Adults aged 18 years and older with select locally advanced or metastatic solid tumor malignancies who have measurable disease. Melanoma, RCC, NSCLC, urothelial carcinoma, TNBC, hormone-receptor-positive breast cancer, gastric cancer, CRC, or SCLC.	**Part 1** (dose escalation) Bempegaldesleukin (mg/kg) + Nivolumab (mg) 0.006 q3w + 240 q2w (n = 4) 0.006 q2w + 240 q2w (n = 3) 0.003 q2w + 240 q2w (n = 3) 0.006 q3w + 360 q3w (n = 25) 0.009 q3w + 360 q3w (n = 3)	Part 1: 50/38 Completed[c]
				Part 2 (RP2D): Bempegaldesleukin 0.006 mg/kg q3w + nivolumab 360 mg q3w	Part 2: 936/476 Ongoing[c]
				Part 3 (Schedule finding for triplet combination) Bempegaldesleukin (mg/kg) + nivolumab (mg or mg/kg), + ipilimumab (mg/kg**)** 0.006 q3w + 360 mg q3w + 1 q6w (n=10) 0.006 q3w + 1 mg/kg × 4 doses q3w + 3 q3w × 4 doses + maintenance 0.006 q3w + 3 mg/kg × 4 doses q3w + ipilimumab 1 q3w × 4 doses + maintenance Maintenance dose: bempegaldesleukin 0.006 mg/kg + nivolumab 360 mg q3w.	Part 3: 36/[24] Ongoing[c]
				Part 4 (RP2D dose expansion for triplet combination): bempegaldesleukin 0.006 mg/kg q3w + nivolumab 360 mg + ipilimumab)	Part 4: 106/19 Ongoing[c]

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
16-214-05 (PROPEL)[f] ~60 sites Dose Optimization: US Dose Expansion: US, Australia, France, Germany, Italy, Spain	A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety and Preliminary Efficacy of NKTR-214 in Combination with Pembrolizumab in Patients with Locally Advanced or Metastatic Solid Tumors (Nektar Therapeutics)	Dose optimization cohorts: • To evaluate the safety and tolerability of bempegaldesleukin in combination with pembrolizumab • To define the MTD/RP2D and optimal dosing schedule of bempegaldesleukin in combination with pembrolizumab Dose expansion cohort: • To determine the ORR by RECIST 1.1 of bempegaldesleukin plus pembrolizumab in patients with untreated metastatic NSCLC	Adults aged 18 years and older with locally advanced or metastatic solid tumors	**Dose Optimization:** **Cohort 1a**: Bempegaldesleukin 0.008 mg/kg (starting dose) + pembrolizumab per PI **Cohort 1b:** Bempegaldesleukin at previously tolerated dose + pembrolizumab per PI (determined by the SRC for step-up dosing schema); dose may increase at each cycle for individual patients (increments of 0.002 mg/kg) per dose optimization schema **Dose Expansion:** Bempegaldesleukin 0.006 mg/kg q3w (starting dose) + pembrolizumab per PI; additional patients may receive dose established by dose optimization cohorts.	Dose Optimization: up to ~40/3 Dose Expansion: ~58/7[g] Ongoing

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
17-262-01 (REVEAL)	A Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-262 in combination with NKTR-214 and in combination with NKTR-214 plus nivolumab in patients with locally advanced or metastatic solid tumor malignancies. (Nektar Therapeutics)	• To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) or RP2D of NKTR-262 in combination with bempegaldesleukin (doublet) and the safety and tolerability of NKTR-262 and bempegaldesleukin plus nivolumab (triplet). • To evaluate the anti-tumor activity of the combination of NKTR-262 plus bempegaldesleukin (doublet) and the combination of NKTR-262 and bempegaldesleukin plus nivolumab (triplet) by assessing the objective response rate (ORR) by RECIST 1.1.	Patients with selected tumor types	Phase 1: Part 1 (dose escalation, ongoing) Planned: NKTR-262 0.03 mg to1.92 mg + bempegaldesleukin 0.006 mg/kg q3w (NKTR-262: 0.03 mg: n=3; 0.06 mg: n=7; 0.12 mg: n=3; 0.24 mg: n=4; 0.48 mg: n=4; 0.96 mg: n=4; 1.92 mg: n=3) NKTR-262 (escalating doses) + bempegaldesleukin 0.006 mg/kg q3w + nivolumab 360 mg q3w. Part 2 (RP2D, dose expansion): Cohorts A and B NKTR-262 RP2D + bempegaldesleukin 0.006 mg/kg q3w. NKTR-262 RP2D + bempegaldesleukin 0.006 mg/kg q3w + nivolumab Phase 2 Doublet regimen: NKTR-262 RP2D + bempegaldesleukin 0.006 mg/kg q3w. Triplet regimen: NKTR-262 RP2D + NKTR-214 0.006 mg/kg q3w + nivolumab 360 mg q3w.	Phase 1: 48 Phase 2: ~400 36 enrolled as of 27 Mar 2020 Ongoing

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
Phase 2 Studies					
18-214-10/ CA045-012 (PIVOT-10)[h] ~100 Global	A Phase 2, single-arm study of bempegaldesleukin (NKTR-214) in combination with nivolumab in cisplatin ineligible, locally advanced or metastatic urothelial cancer patients (Nektar Therapeutics)	To evaluate the anti-tumor activity of bempegaldesleukin (NKTR-214) in combination with nivolumab by assessing the ORR by RECIST v1.1 per BICR in patients whose tumors have low PD-L1 expression	Patients with locally advanced or metastatic urothelial cancer that are cisplatin ineligible and previously untreated	Bempegaldesleukin 0.006 mg/kg and nivolumab 360 mg q3w	190/129[i]
Phase 3 Studies					
CA045-001/ 17-214-08 (PIVOT-IO-001) 130 sites US, Australia, New Zealand, Canada, France, Italy	A Phase 3, Randomized, Open-label Study of NKTR-214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma (Bristol Myers Squibb)	• To compare the ORR using RECIST v1.1 of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma • To compare PFS using RECIST v1.1 of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	Adult and adolescent (≥12 years of age) participants with previously untreated unresectable or metastatic melanoma (AJCC stage III or stage IV).	**Arm A:** Bempegaldesleukin 0.006 mg/kg q3w+nivolumab 360mg q3w(sequential) **Arm B:** Nivolumab 360 mg q3w	764/258[j] Ongoing

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
		• To compare OS of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma			
17-214-09/ CA045002 (PIVOT-09)[k] ~150 sites Global	A Phase 3 Randomized Open Label Study to Compare NKTR-214 Combined with Nivolumab to the Investigator's Choice of Sunitinib or Cabozantinib in Patients with Previously Untreated Advanced Renal Cell Carcinoma (Nektar Therapeutics)	• To compare the ORR by BICR assessment using modified RECIST v1.1 of bempegaldesleukin (NKTR-214) combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC • To compare the ORR by BICR using mRECIST v1.1 of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC • To compare the OS of bempegaldesleukin combined with	Patients aged 18 years and older with advanced or metastatic, histologically confirmed RCC (advanced RCC) with a clear-cell component, who have not received prior therapy for the treatment of RCC.	**Arm A:** Bempegaldesleukin 0.006 mg/kg q3w + nivolumab 360 mg q3w **Arm B:** Investigator's choice of either one of the following treatments: Sunitinib 50 mg orally (po) once daily for 4 weeks followed by 2 weeks off OR Cabozantinib 60 mg po once daily	600/277[l] Ongoing

Protocol ID Number of Study Sites and Location	Protocol Title and Design (Sponsor)	Primary Objective(s)	Study Population	Dosing Regimen	Number of Patients Planned/Enrolled Status
		nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC • To compare the OS of bempegaldesleukin combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC			
CA045-009/ 18-214-13 (PIVOT-IO-009) ~ 120 sites	A Phase 3, Randomized, Study of Neoadjuvant and Adjuvant Nivolumab Plus NKTR-214, Versus Nivolumab Alone Versus Standard of Care in Participants with Muscle-Invasive Bladder Cancer (MIBC) Who Are Cisplatin Ineligible (Bristol Myers Squibb)	• To compare the pCR rate of neoadjuvant nivolumab + NKTR-214 to Standard of Care (SOC, no neoadjuvant therapy) in all randomized participants • To compare the EFS of neoadjuvant nivolumab + bempegaldesleukin followed by adjuvant nivolumab + bempegaldesleukin after radical cystectomy (RC) versus SOC (no neoadjuvant or adjuvant therapy)	Patients, aged 18 years or older with previously untreated MIBC who are cisplatin ineligible.	**Arm A:** Bempegaldesleukin 0.006mg/kg q3w + nivolumab 360 mg q3w x 3 cycles as neoadjuvant therapy, followed by radical cystectomy, followed by bempegaldesleukin 0.006mg/kg q3w + nivolumab 360 mg q3w up to an additional 12 cycles (approximately 9 months of adjuvant therapy). **Arm B:** Nivolumab 360 mg q3w x 3 cycles as neoadjuvant therapy, followed by radical cystectomy, followed by nivolumab 360 mg q3w up to an additional 12 cycles (approximately 9 months of adjuvant therapy). Arm C: Standard of care (cystectomy alone, without neoadjuvant or adjuvant therapy)	Approximately 720 participants will be screened for approximately 540 participants to be randomized /2^m Ongoing

Abbreviations: ~=approximately; AST= aspartate aminotransferase; BICR=blinded independent central review; CRC= colorectal cancer; ECG=electrocardiogram; EoA= end of administration; FDBK=FujiFilm UK; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MIBC= muscle-invasive bladder cancer; MTD= maximum tolerated dose; NSCLC=non-small cell lung cancer; ORR= objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; PK=pharmacokinetic; q3w=every 3 weeks; RCC=renal cell carcinoma; RECIST= Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; SCLC= small cell lung cancer; SRC=Safety Review Committee; TKI=tyrosine kinase inhibitor; TNBC=triple-negative breast cancer; v1.1=version 1.1

a. The planned Phase 2 dose expansion part of the study was not conducted, per Sponsor decision. Enrollment was discontinued after 28 patients were enrolled in the dose-escalation part of the study and the MTD determined to allow the clinical development program for bempegaldesleukin to continue with other studies in which NKTR-214 is administered in combination with checkpoint inhibitors.
b. Based on Amendment 7.0.
c. Study 15-214-02 (PIVOT-02) was closed to enrollment and screening on 22 January 2010; last patient enrolled on 29 January 2020.
d. Based on mono-SPC level in Drug Substance Lot 1-PRO-0526 (46%), which constitutes 73% of Drug Product Lot 1-FIN-2590.
e. Based on mono-SPC level in Drug Substance Lot 1-PRO-0783 (32%), which constitutes 72% of Drug Product Lot 1-FIN-2881.
f. Based on Amendment 5.0, dated 20 August 2019.
g. Enrollment as of 25 March 2020
h. Based on Amendment 4.0, dated 06 February 2020.
i. Enrollment as of 26 March 2020
j. Enrollment as of 26 March 2020.
k. Based on Amendment 2.0, dated 03 February 2020.
l. Enrollment as of 26 March 2020
m. Enrollment as of 26 March 2020