Nektar Therapeutics

STATISTICAL ANALYSIS PLAN

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

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ABBREVIATIONS

Abbreviation	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)
ATC	Anatomical Therapeutic Chemical
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
BLQ	below the limit of quantification
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
CV%	coefficient of variation(%)
DCI	data collection instrument
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
ECG	electrocardiogram

Abbreviation	Term Definition
ECLA	electrochemiluminescence assay
eCOA	electronic clinical outcomes assessments
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
FiO2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
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 Harmonization
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

Abbreviation	Term Definition
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
mg	milligram
min	minute(s)
mL	milliliter
mm Hg	millimeters of mercury
msec	millisecond
MTD	maximum tolerated dose
NaCl	sodium chloride
NCA	noncompartmental analysis
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
PD-L1	programmed cell death ligand 1
PE	pulmonary embolism
PEG	polyethylene glycol
PK	pharmacokinetic
Q1	first quartile
Q3	third quartile
q3w	every 3 weeks
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human interleukin-2
RT-PCR	reverse transcription polymerase chain reaction

Abbreviation	Term Definition
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
SD	Standard deviation
SEM	standard error of mean
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
WHO-DDE	WHO Drug Dictionary Enhanced
WOCBP	Women of childbearing potential

1.0 INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Nektar Therapeutics Protocol 20-214-34 "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". The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- 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.

2.2 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 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.
- 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.

3.0 STUDY DESIGN AND PLAN

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 Protocol 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 Protocol 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 Protocol 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.

4.0 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. It is expected that a total of approximately 30 patients will be enrolled into the study.

5.0 GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables and data listings. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of patients in

corresponding categories. All summary tables will be presented by treatment. For patients who receive placebo, the data will be pooled as one placebo group.

Individual subject data obtained from the case report forms (CRFs) and any derived data will be presented by subject in data listings. Data listings will be sorted by the treatment group, subject, visit date, and time, if applicable.

All analyses and tabulations will be performed using SAS Version 9.4 or higher. All outputs will be presented in rich text format (RTF).

5.1 Definition of Common Variables

- Reference date (Day 1) = first dose date of study medication. If a patient has not been treated, the reference day will be set as missing.
- Study Day = assessment date – reference date + 1 for assessments performed on or after the reference date or assessment date – reference date for assessments performed before the reference date.
- Baseline: Baseline will be defined as the last non-missing value on or before the date of administration of the first dose of study medication (and time if available) unless it is identifiable by time that the value is after the first dose. For patients who have been not treated with any dose, then the baseline is defined as the screening value.

Time on study will be calculated as follows:

For visits/assessments/medications/therapies on or post study drug:

- Study hour will be calculated as follows:
- Study Hour = (assessment date time – date time of the start of the first study dose)/60
- Study Day = (assessment date – date of the first study dose) + 1, if assessment date is on or after the study dose date in that cohort
- Study Day = (assessment date – date of the first study dose), if assessment date is prior to the study dose date in that cohort

For visit window derivation purpose, Study Day will be derived as ceiling of (Study Hour)/24.

For purposes of analysis and data display (i.e., means over time), actual visit hours/days are mapped to the planned study visit (i.e., nominal visits such as Hour 1, 2, Day 2, etc.) using visit windows. Acceptable visit windows around each scheduled procedure visit will be given for each measurement in the forthcoming sections. Due to the different data collection schedules for the various measurements, however, visit windows for different parameters might not be identical.

Unless otherwise specified, in mean and mean change from baseline/pre-dose summaries or analyses, if more than one value is obtained for the same measure within a given visit window,

the value closest to the planned study visit day and/or time will be used for reporting and analysis. If multiple values are equally away from the nominal visit day and/or time, the latter one will be used. However, for shift tables, the worst value mapped to that visit window will be used for summary purposes.

5.2 Handling Missing Data

Missing data will be handled as follows:

- For prior systemic cancer therapies and medical history of cancer, the study day corresponding to the start and stop date of the regimen will be calculated when calculating duration of the therapy/history and relevant time to the first study dose, etc. For partially missing start dates, missing day of the month will be imputed as the first of the month and missing month will be imputed as January. For partially missing stop dates, missing day of the month will be imputed as the last day of the month and missing month will be imputed as December and at least 1 day after the start date. No imputation will be done if the year is missing.

For the duration of AEs, AE start date with missing month and year and AE stop date with missing year will not be imputed.

In general, no imputation will be considered for missing date or partial dates with the following exceptions:

- For duration of AEs, partially missing dates for start of AE, will be imputed as follows:
    - Start day of AE is missing
        - If the reported month of occurrence of the AE is after the study dose, then day will be imputed as the first day of the month of occurrence of AE.
        - If the reported month of occurrence of the AE is the current month as the dose, then the missing day will be imputed as the same day as study dose date.

- For duration of AEs, a partially missing stop date of the AE will be imputed as follows:
    - If the month is missing, but year is present, either 31st December, the date of discontinuation from the study, or the date of death, whichever is earlier, will be used as the stop date.
    - If the day is missing, but year and month are present, either the last day of that month, the date of discontinuation from the study, or the date of death, whichever is earlier, will be used as the stop date.

Some laboratory analytes may be reported by range (e.g., gamma-glutamyl transferase [GGT] < 17 U/L) and will be imputed by the corresponding boundary (e.g., 17 U/L).

6.0 ANALYSIS POPULATIONS

Screened patients: All patients who signed study participation informed consent.

Enrolled patients: All patients who are assigned/randomized to either the bempegaldesleukin/SOC or placebo/SOC treatment groups.

Safety/Treated Population: All patients who receive at least 1 dose (full or partial dose) of study drug.

Pharmacokinetic Population: All patients in the Safety Population with at least one measurable concentration.

Immunogenicity Population: All patients in the Treated Population with at least baseline and one post-baseline ADA assessment.

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7.0 STATISTICAL ANALYSIS

7.1 Subject Disposition

Subject disposition information will be summarized for all patients. Summaries will include: the number and percentage of patients in each analysis population, the number and percentage of patients who completed the study, and the number and percentage of patients who discontinued the study and the reason for discontinuation. All patients randomized/enrolled in the study will be included in the summary table.

7.2 Important Protocol Deviations

Important protocol deviations are a subset of the protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Final list of the important protocol deviations and the associated categories will be determined by the study team before the database lock.

The number and percentage of patients in each important protocol deviations category and sub-category will be summarized by treatment group and total. All protocol deviations will be listed.

7.3 Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, and race. Other baseline characteristics include height, weight, calculated body mass index (BMI), and vital signs. Demographic and baseline characteristics will be summarized for the Treated Population.

Age will be calculated as:

Integer [(Date informed consent signed – Date of birth) / 365.25].

BMI will be calculated as:

Weight (kg) / Height (m^2).

7.4 Prior and Concomitant Medications and Procedures

Prior and concomitant medications will be coded to ATC level and preferred drug name using WHO-DDE.

Prior medications are defined as medications taken starting prior to the first dose. Prior medications will be summarized for the Treated Population using the same analytical procedures as concomitant medications. Concomitant medications are defined as medications taken on or after the date of first study dose, including medications initiated prior to the date of first dose and continued during treatment, and medications initiated on or after the date of first dose, but before the last study dose + 30 days or start of subsequent anticancer therapy, whichever is earlier.

Concomitant medications will be tabulated for the Treated Population by WHO-DDE ATCL-2 classifications and preferred term. If the ATCL-2 classifications is missing, the next non-missing higher level of classification will be used (Level 1). If a patient reports the same medication multiple times, then the frequency reported for that medication will be incremented by only one. As with the medication, if a patient reports multiple medications within the same ATCL-2 classification then the frequency for that ATCL-2 classification will be incremented by only one. Percentages will be calculated using the total number of patients in the Treated Population.

Prior and concomitant medications will also be presented in a data listing.

7.5 Study Treatment Exposure

Total dose administered (mg, mg/kg) will be summarized by N (observed), mean, SD, median, Q1, Q3, min, and max for each bempegaldesleukin dose level in Treated Population. Number and percentage of patients with full dose will be provided for each bempegaldesleukin dose level and total in the Treated Population.

7.6 Efficacy Analyses

7.6.1 Analysis of Percentage of Patients Who Require Supplemental Oxygen

Number and percentage of patients who require supplemental oxygen will be provided by treatment group and total for Treated Population.

7.6.2 Analysis of Shift from Baseline to Post-Baseline in Clinical Status

Shift from baseline to post-baseline clinical status based on the World Health Organization (WHO) Clinical Progression Scale will be provided for patients with no change, with 1, 2, and ≥3 points of improvement or worsening in the Treated Population. The 10-point WHO Clinical Progression 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

7.6.3 Analysis of Clinical Status Based on the WHO Clinical Progression Scale on Days 3, 5, 8

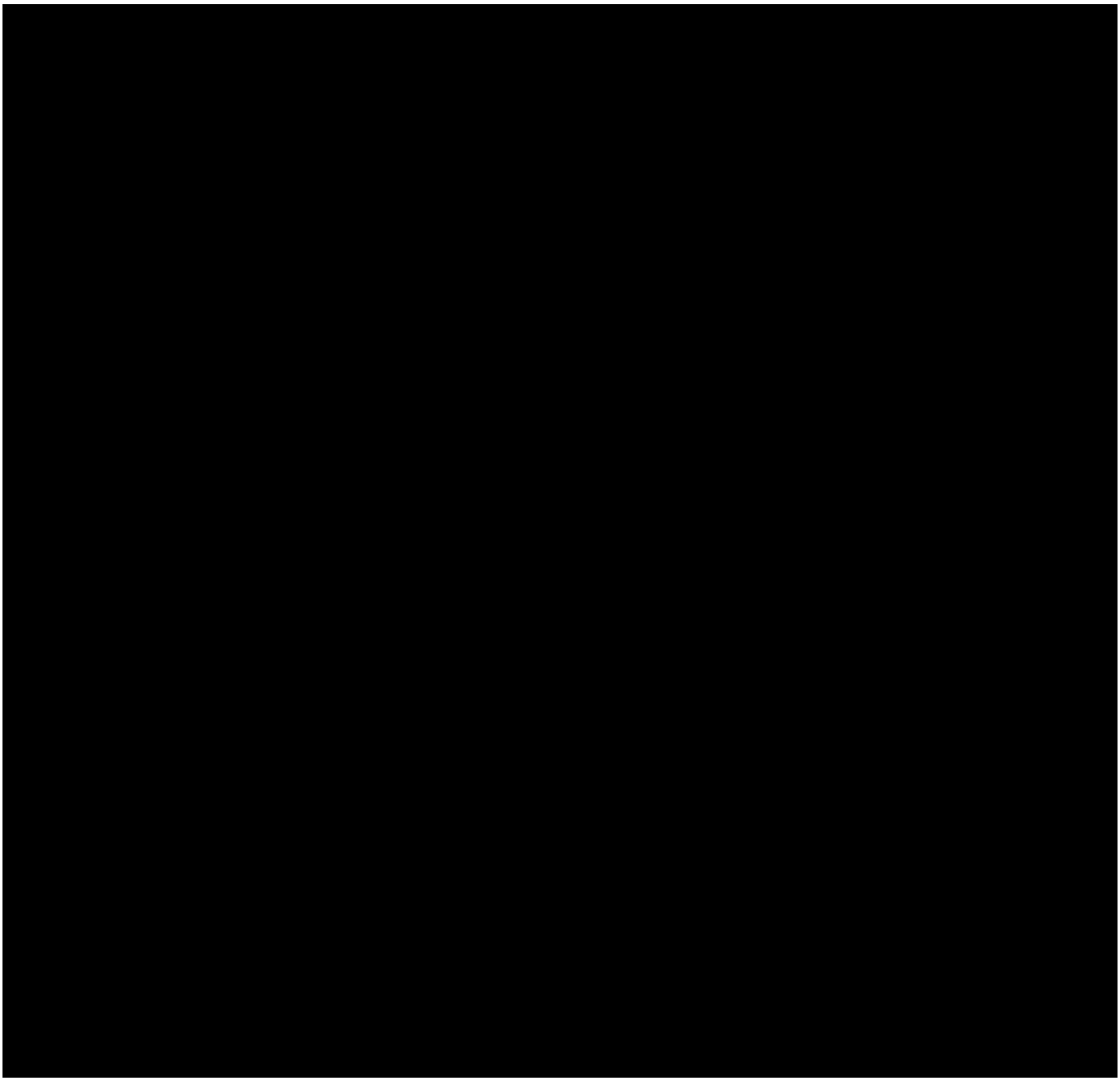
Number and percentage of patients will be provided for each clinical status (i.e. WHO progression scale point) on Days 3, 5, and 8 by treatment group and total.

7.6.4 Analysis of Number of Days Receiving Supplemental O_2, Non-Invasive, High-Flow, Mechanical Ventilation, ECMO

Oxygen days are defined as days where the clinical status score is equal to 5, 6, 7, 8, or 9. The total number of oxygen days is the sum of all reported oxygen days.

Number of oxygen days will be summarized by N (observed), mean, SD, median, Q1, Q3, min, and max for each treatment group and total in Treated Population. Number and percentage of

patients will be provided for number of oxygen days by treatment group and total in Treated Population, if deemed necessary.



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9.0 PHARMACOKINETIC ANALYSES

Listings for blood collection dates, times and concentrations will be generated by patient for each analyte. Sampling time deviations will be computed as differences between scheduled (nominal) and actual sampling times and expressed in hours and as a percentage of the nominal time.

Observed plasma NKTR-214-RC (bempegaldesleukin-related molecules; mixture of compounds containing IL-2 independent of PEG conjugation status) at each nominal PK sampling time will be tabulated using descriptive statistics, including but not limited to N (number of non-missing data), N (missing), arithmetic mean, standard deviation (SD), standard error of the mean (SEM), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum.

Individual and overlay plots of observed plasma NKTR-214-RC concentration-time profiles will be generated on linear and semi-logarithmic scales using actual times.

Plots of mean (+ standard deviation) observed plasma NKTR-214-RC concentrations versus nominal time will be generated on linear and semi-logarithmic scales based on nominal sampling times.

PK samples that were collected outside the protocol accepted time windows will be excluded from summary tables and summary figures.

The PK analyses will use Quality Assured (QA) final bioanalytical data. Missing concentration values will not be imputed. When summarizing concentrations, zero values will be excluded from the calculation of geometric means and CV% geometric mean, however, they will be included for all other summary statistics and the number of non-zero concentrations will be reported. Missing values for any PK parameters will not be imputed and will be handled as missing.

When calculating PK parameters, all Cycle 1 pre-dose concentrations that are below the limit of quantification (BLQ) will be set to 0; all other concentrations that are BLQ will be set to missing for calculation of PK parameters and will be set to 0 for summary statistics.

PK parameters will be derived by Phoenix WinNonlin (version 8.3 or higher) based on noncompartmental (NCA) methods. PK parameters (Error! Reference source not found.) will include C_{max}, T_{max}, AUC_{last}, AUC_{inf}, V_z, CL, and $t_{1/2}$ for NKTR-214-RC. Time zero will be

defined as the start time of the infusion. Linear-up/log-down NCA methods will be used to estimate AUC.

NCA PK parameters listed in

Table 2: will only be derived when all specified requirements are met. Where requirements are not met, PK parameter values will be reported as "not determinable".

Table 1: Pharmacokinetic Parameter Definitions

PK Parameter	Description
AUC_{inf}	Area under the concentration-time curve calculated from time 0 to infinity
AUC_{last}	Area under the concentration-time curve calculated from time 0 to the last measurable concentration
$AUC_{0\text{-}96h}$	Area under the concentration-time curve calculated from time 0 to 96 hours after dosing
$AUC_{0\text{-}168h}$	Area under the concentration-time curve calculated from time 0 to 168 hours after dosing
CL	Systemic clearance
C_{max}	Maximum observed concentration following study drug administration
$t_{1/2}$	Half-life: the time required for the concentration to reach half of its original value
T_{max}	Time to reach maximum concentration
V_z	Volume of distribution during the terminal elimination phase following intravenous administration

Table 2: Noncompartmental Analysis Requirements

PK Parameter	Requirement
$t_{1/2}$, AUC_{inf}, CL, V_z	A minimum of 3 time points should be used for determining lambda_z, not including the C_{max} time point. The span of the terminal phase must be at least 2 times the half-life for lambda_z to be determined. Where Rsq_adj < 0.75, lambda_z will not be determined If lambda_z is not determined then $t_{1/2}$, AUC_{inf}, CL, or V_z will not be reported.
AUC_{inf}	The extrapolated area should not contribute more than 20% to the total AUC_{inf} for the estimation of AUC_{inf}

PK parameters will be listed by patient and summarized using descriptive statistics, including but not limited to N (observed), geometric mean, mean, SEM, SD, CV%, geometric CV%, median, minimum and maximum. PK parameters will be summarized for each treatment group. T_{max}, CL, $t_{1/2}$, and V_z will also be summarized in total Treated Population.

Rounding for the reporting of PK parameters will be to three significant digits. Percentages such as CV% presented in tables will be rounded to one decimal place. The same convention will be followed for descriptive statistics, except for n, which will be rounded to the whole value.

10.0 IMMUNOGENICITY ANALYSES

10.1 Immunogenicity

Validated methods to detect anti-bempegaldesleukin, anti-PEG and anti-IL-2 anti-drug antibodies (ADA) will be used to analyze immunogenicity samples. Serum samples will be analyzed by multi-tiered ADA testing as per the 2019 FDA guidance (FDA 2019). Immunogenicity sample testing will be done in tiers. Samples will be first tested with screening electrochemiluminescence assays (ECLA). Putative positive samples for anti-bempegaldesleukin or anti-IL-2 antibodies will then be analyzed in competition ECLA to confirm positivity. Confirmed anti-bempegaldesleukin antibodies-positive samples will be tested further in a polyethylene glycol (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 each assay (anti-bempegaldesleukin and anti-IL-2) will then be tested to obtain a titer. Samples confirmed to be positive for anti-bempegaldesleukin and anti-IL-2 antibodies will also be tested for neutralizing activity for IL-2 using a validated cell-based assay. The data will be summarized for anti-bempegaldesleukin, anti-PEG, anti-IL-2 antibodies and will be reported by sample and patient status.

For sample status, immunogenicity data will be summarized by the number and percentage of confirmed anti-drug antibodies (ADA) to bempegaldesleukin, PEG, IL-2 by analyte and visit. The samples will be classified as baseline ADA-positive, if ADA is detected in the immunogenicity sample collected before initiation of the treatment and baseline ADA-negative, if ADA is not detected in the immunogenicity sample collected before initiation of the treatment. ADA samples will be classified as positive if after initiation of the treatment, the ADA is detected in a sample from a subject who was baseline negative, or if there is at least 4-fold or greater (≥) increase in ADA titer in comparison to the baseline positive titer.

For patient status, immunogenicity will be reported by summarizing the number and percentage of ADA-positive patients and ADA-negative patients at baseline and after drug administration with positive status of anti-bempegaldesleukin, anti-PEG, anti-IL-2 ADA. In the immunogenicity evaluable population, the patients will be classified as treatment-induced ADA-positive if they were ADA-negative at baseline and became ADA-positive at any time after starting the treatment, or if they were ADA-positive at baseline and had a post-baseline ADA-positive titer that was at least 4-fold or greater (≥) than baseline positive titer (Treatment-boosted). Treatment-emergent ADA-positive patients will be the sum of treatment-induced and treatment-boosted ADA-positive patients. Patients with at least one ADA-positive sample with neutralizing activity will be classified as neutralizing positive. All other ADA-evaluable patients are considered as treatment-emergent ADA negative.

10.2 Safety Evaluation of ADA

All patients with ADA as mentioned above will be assessed for infusion related reactions (including hypersensitivity/angioedema/anaphylaxis) and will be compared against ADA negative patients.

10.3 Definitions

There are two sets of definitions: one for categorizing individual samples in Table 3 and another for categorizing patient responses in Table 4.

Table 3: ADA Status: Individual Samples

ADA Status	Definition
Baseline Negative	ADA is not detected in the last sample before initiation of treatment
Baseline positive	ADA is detected in the last sample before initiation of treatment
Anti-bempegaldesleukin ADA-positive sample	After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a patient for whom anti-bempegaldesleukin ADA is not detected at baseline, *or* (2) an ADA detected sample with anti-bempegaldesleukin titer to be at least 4-fold or greater (≥) than baseline positive titer
Anti-PEG ADA-positive sample	Sample with a positive result in PEG -specificity assay.
Anti-IL-2 ADA-positive sample	After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a patient for whom anti-IL-2 ADA is not detected at baseline, *or* (2) an ADA detected sample with anti-IL-2 titer to be at least 4-fold or greater (≥) than baseline positive titer

Table 4: ADA Response Categories: Patient Level

ADA status	Description
Baseline ADA-positive	A patient with baseline ADA-positive sample
ADA-Negative Patient	Patient with no ADA-positive sample after the initiation of treatment. **Note:** due to the definition of an ADA positive sample for a patient testing positive at baseline (see sample status table, above), it is possible (but highly unlikely) for a patient with a stable anti-drug titer throughout the study to be classified as 'ADA-negative'
ADA-Positive Patient (Treatment-Emergent positive)	Patient with at least 1 ADA positive-sample (relative to baseline) at any time after initiation of treatment
Neutralizing positive	At least 1 ADA-positive sample with neutralizing antibodies detected

11.0 SAFETY ANALYSES

All safety analyses will be based on the Safety Population.

11.1 Analysis of Dose-Limiting Toxicity

Dose finding for this study is based on the assessment of dose-limiting toxicity (DLT) of bempegaldesleukin dose levels. Number and percentage of patients with any DLT will be summarized by bempegaldesleukin dose level in bempegaldesleukin/SOC treatment groups and placebo for the Safety Population.

11.2 Adverse Events

An AE is defined as any untoward medical occurrence in a subject who is administered a medicinal product and that does not necessarily have a causal relationship to the treatment. All AEs will be included in the data listings. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0).

A Treatment-Emergent Adverse Event (TEAE) is defined as an adverse event that occurs on or after the treatment dose, and treatment-emergent period is from the study dose date to 30 days after the study dose. The TEAE summary will be displayed by treatment using treatment-emergent period. Unless otherwise specified, summaries that are displayed by SOC and preferred terms will be ordered alphabetically by SOC, and within each SOC, preferred terms will also be ordered alphabetically. Summaries of the following types will be presented:

- TEAEs by MedDRA SOC and preferred term.
- TEAEs by MedDRA SOC, preferred term, and worst CTCAE grade (version 5.0). At each level of subject summarization, a subject is classified according to the worst CTCAE grade if the subject reported one or more CTCAE grade.
- TEAEs related to study drug by MedDRA SOC, preferred term, and worst CTCAE grade.
- TEAEs by descending incidence of preferred terms.
- Serious TEAEs by MedDRA SOC, preferred term and worst CTCAE grade.
- Serious TEAEs related to study drug by MedDRA SOC, preferred term, and worst CTCAE grade.
- TEAEs leading to early termination by MedDRA SOC, preferred term, and worst CTCAE grade.
- Any Grade ≥ 3 drug-related AE.
- Respiratory compromise or other virus-related AE attributed to worsening COVID-19, such as severe hypoxia, cyanosis, or chest pain/pressure.
- TEAEs leading to deaths.

For each subject and for each adverse event, the duration of the event (days) will be calculated as:

Duration of AE (Days) = AE stop date – AE start date +1.

The duration of AEs will be displayed in the data listing.

11.3 Medical History

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.

Medical history will be listed and summarized by System Organ Class and Preferred Term.

11.4 Visit Window for Safety Endpoints:

If more than one value is obtained for the same measure within a given visit window, the value closest to the planned study visit day/time will be used for reporting and analysis. If multiple values are the same number of days/times away from the nominal visit day/time, the latter one will be used.

11.5 Clinical Laboratory Evaluation

Hematology and chemistry parameters will be summarized using descriptive statistics at baseline and post-dose. Changes from baseline will also be summarized.

Shift tables will be provided to assess changes in laboratory values from baseline to worst post-dose CTCAE grade. Only non-missing assessments at baseline and post-dose will be analyzed.

Any clinically significant lab abnormalities will be determined by the Principal Investigator and will be reported in the AE table summaries.

11.6 Vital Signs

Vital signs, including oxygen saturation (SpO_2), will be summarized using descriptive statistics at baseline and at each post-dose time point. Changes from baseline will also be summarized using descriptive statistics.

11.7 Electrocardiogram

ECG parameters (numeric) at baseline will be summarized using descriptive statistics.

The number and percentage of patients with abnormal (not clinically significant or clinically significant) and number and percentage of patients in each of the following categories based on QTcF at baseline will be provided in the safety Population:

- QTc interval ≤ 450 ms,
- QTc interval > 480 ms,
- QTc interval > 500 ms.

12.0 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

No changes from the protocol-specified analyses are planned.

13.0 REFERENCES

1. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020; https://doi.org/10.1016/S1473-3099(20)30483-7.