STATISTICAL ANALYSIS PLAN

Study Name: XPORT-CoV-1001

A Phase 2 Randomized Single-Blind Study to Evaluate the Activity and Safety of Low Dose Oral Selinexor (KPT-330) in Patients with Severe COVID-19 Infection

Protocol Number:	XPORT-CoV-1001
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By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol and all applicable regulatory guidance and guidelines.

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AT	all-treat
ATC	Anatomical Therapeutic Class
CCI [redacted]	
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CP	Conditional power
CCI [redacted]	
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DR-14	Overall death rate on Day 14
DR-28	Overall death rate on Day 28
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EE	Efficacy evaluable
FiO2	Fraction of Inspired Oxygen
IA	Interim Analysis
ITT	Intent-to-Treat
ICU	intensive care unit
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
NSAID	nonsteroidal anti-inflammatory drug
PaO2	Partial Pressure of Oxygen in Arterial Blood
PT	Preferred Term
OS	Overall survival
OSI-14	Day 14 Ordinal Scale improvement
OSI-28	Day 28 Ordinal Scale improvement
QTcF	QT Interval Corrected For Heart Rate Using Fridericia's Formula

RMV	Rate of mechanical ventilation
SAP	Statistical Analysis Plan
SSR	sample size re-estimation
STD	standard deviation
TEAE	Treatment Emergent Adverse Event
TTMV	Time to mechanical ventilation
TTCI	Time to Clinical Improvement
TTR	Time to recovery
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan describes detailed statistical methods to be used for analysis and data presentation for reporting the activity and safety of low dose oral selinexor (KPT-330) in patients with severe coronavirus disease 2019 (COVID-19).

This document has been prepared according to study protocol version 7.0 dated 18 June 2020.

2. STUDY DESIGN

2.1 Overview of Study Design

This is a randomized phase 2 single-blinded study of low dose selinexor versus placebo to evaluate the activity and safety, as well as reduction in mortality in patients with severe COVID-19.

A dose of 20 mg selinexor or matching placebo will be administered orally on Days 1, 3, and 5 of each week for up to 2 weeks. If the patient is tolerating therapy and clinically benefitting, dosing can continue for an additional 2 weeks.

The study population will consist of hospitalized patients ≥18 years old with COVID-19.

The randomization under protocol version 6.0 or above will be stratified by:

- Use of concomitant therapies
  - Use of anti-viral (e.g. remdesivir) only
  - Use of anti-inflammatory (e.g. hydroxychloroquine, biologics targeting e.g. IL-6 or IL-1) only
  - Use of both anti-viral and anti-inflammatory therapies
  - Use of neither anti-viral nor anti-inflammatory therapy
- Number of high-risk comorbidities.
  - No high-risk comorbidity
  - One high-risk comorbidity
  - Two or above comorbidities

High risk comorbidities are defined as: BMI> 30, cancer patients on chemotherapy, patients with cardiac (CAD, AMI, CHF) or pulmonary (COPD, emphysema) disease, diabetes, hypertension.

Note: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) will not constitute anti-inflammatory agents for the purposes of stratification.

The study schedules are presented in Table 1 of the protocol.

2.2 Sample Size and Power Considerations

Approximately 300 patients are planned to be enrolled:

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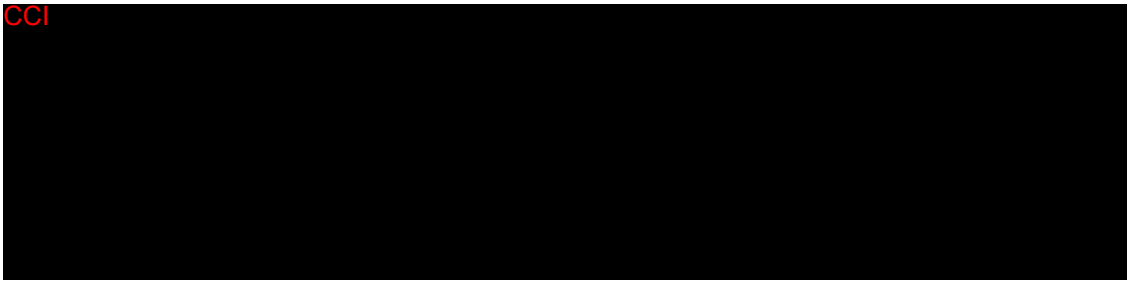


2.3 Interim Analyses

The interim analyses apply to ITT population only.

The first IA occurs 14 days after the first 74 patients are randomized. This IA is for futility only (non-binding). The futility boundary p-value will be calculated using the Lan DeMets spending function with the O'Brien-Fleming type of boundary based on the actual number of patients who have completed 14 days on study at the time of the IA.

The second IA happens 14 days after 124 patients are randomized. This IA is for futility and sample size re-estimation (SSR). An unblinded SSR is planned to be performed at this IA. The unblinded SSR will be based on the method of conditional power (CP). It is defined as the probability to detect a statistically significant difference for the primary endpoint at the end of study given the current data observed during this second IA, assuming this interim trend continues. The CP will be calculated for the primary endpoint at this IA using East software with CHW method (Cui et al., 1999).

The odds ratio and associated p-value will be obtained for the primary efficacy endpoint between two treatment arms based on the observed data at this IA, then the CP will be calculated using East. The calculated CP will be assigned to one of the 3 zones:

1. favorable (CP ≥80%)

2. promising (30% ≤ CP <80%)

3. unfavorable (CP< 30%)

Additionally, if the 2nd interim analysis is conducted and sample size is adjusted, the CHW method (Cui et al., 1999) will be implemented in the primary analysis for the primary and key secondary efficacy endpoints to preserve the overall type I error.

Please refer to Section 9.5 in Protocol for Criteria for Stopping the Study.

3. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are described in **Error! Reference source not found.** below.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	
Day 14 Ordinal Scale improvement	Proportion of patients with at least a 2-point improvement (increase) in the Ordinal Scale from time of randomization (baseline) to Day 14. The Ordinal Score is an assessment of the clinical status at the first assessment on each day of hospitalization. The scale is as follows: 1. Death; 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7. Not hospitalized, limitation on activities and/or requiring home oxygen; 8. Not hospitalized, no limitations on activities.
Key Secondary Objectives	
To evaluate improvement in clinical measures across the 2 treatment arms	• Time to an improvement of 2 point using Ordinal Scale (TTCI-2) • Overall Death Rate on Day 28 • Rate of mechanical ventilation

	• Time to mechanical ventilation
Additional Secondary Objectives	
To evaluate improvement in additional clinical measures across the 2 treatment arms	• Time to recovery defined as improvement from baseline score of 3 to ≥4 or from a baseline score of 4 to ≥5 • Proportion of patients with at least a 2 point improvement (increase) in the Ordinal Scale from baseline to Day 7. • Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 7 • Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 14. • Time to an improvement of 1 point on the Ordinal Scale (TTCI-1) • Overall Survival • Overall death rate on Day 14 • Rate of ICU admission • Length of hospitalization • Length of ICU stay • Duration of mechanical ventilation • PaO_2:FiO_2 and/or oxygenation index over time
To determine the anti-inflammatory and immune effect of selinexor	• Reduction of C-reactive protein (CRP) • Reduction in ferritin levels • LDH • Measure changes from baseline of blood plasma cytokines: IL-1β, IL-1Rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IFNγ, IP10, TNFα
To assess safety and tolerability of selinexor [time frame: up to 28 days]	• Listing and documentation of frequency and severity of adverse effects

To characterize selinexor pharmacokinetics	• Selinexor PK parameters, maximum plasma concentration (C_{max}) and trough concentration (C_{trough}), if feasible
Exploratory Endpoints	
CCI [redacted]	

4. GENERAL STATISTICAL METHODS AND DATA HANDLING CONVENTION

4.1 General Statistical Methods

All statistical analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA)

Categorical variables will be tabulated as number of patients and percentage of total number of patients in the given analysis population as noted for each category (with a category for missing data). Percentages will be reported to one decimal place.

Descriptive statistics will be used to summarize continuous variables including number of patients, mean, standard deviation (STD), median, minimum and maximum.

Unless otherwise stated, all analysis will be performed by treatment arm (selinexor versus placebo). Listing will be sorted by treatment arm, patient ID and visit whenever it is applicable.

4.2 Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as number of days relative to the Study Day 1 which is defined as the date of first study treatment (selinexor or placebo for patients in the selinexor or placebo arm respectively), and the preceding day is Day -1, the day before that is Day -2, etc.

- For assessments on/after Study Day 1, study days are calculated as
  (date of assessment – date of Study Day 1 + 1)
- For assessments before Study Day 1, study days are calculated as
  (date of assessment – date of Study Day)

4.3 Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to the first administration of study treatment. Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

4.4 Missing Data Handling Rules

Unless otherwise stated, missing data will not be imputed.

4.4.1 Handling of Missing/partial Dates for Adverse Events or Concomitant Medications

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible.

Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings. In data listings, an ongoing flag will be identified from the eCRF AE page.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book version 1.0 for details on imputation methods.

4.4.2 Handling of Missing or Partial Birth Date for Calculation of Age

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book version 1.0 for details on imputation methods.

4.4.3 Handling of Missing Severity of AEs

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences with the same PT and same patient will be considered. If the severity is missing for all the occurrences or the PT is missing, a "missing" category will be added in the summary table.

4.4.4 Handling of Missing Assessment of Relationship of AEs to Study Treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment in the frequency tables is considered as related.

4.5 Visit Windows

For safety data that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to the nearest visit. Analysis visit windows for clinical laboratory parameters are defined in Table 2 to Table 4. If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, then select the latest one for the analysis. Visit windows definitions will be described in analysis data specifications.

Table 2: Visit Windows for CBC with differential, Complete serum chemistry, C-reactive protein, Ferritin and LDH.

Analysis Visit Name	Target Visit Day	Study Day Range in Window

Baseline	Day 1	Prior to first dosing (prior to or on Day 1 if exact dosing time is not available)
Day 3	Day 3	Day 2 to 3
Day 5	Day 5	Day 4 to 6
Day 8	Day 8	Day 7 to 9
Day 12	Day 12	Day 10 to 13
Day 15	Day 15	Day 14 to 16
Day 19	Day 19	Day 17 to 20
Day 22	Day 22	Day 21 to 23
Day 26	Day 26	Day 24 or later
NOTE: Day 1 is the date of first selinexor or placebo. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 3: Visit Windows for PT, aPTT, INR, CCI [redacted].

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to first dosing (prior to or on Day 1 if exact dosing time is not available)
Day 3	Day 3	Day 2 to 3
Day 5	Day 5	Day 4 to 6
Day 8	Day 8	Day 7 to 9
Day 12	Day 12	Day 10 to 13
Day 15	Day 15	Day 14 to 18
Day 22	Day 22	Day 19 to 23
Day 26	Day 26	Day 24 or later
NOTE: Day 1 is the date of first selinexor or placebo. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 4: Visit Windows for Cells for Leukocyte Phenotyping

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 4
Day 8	Day 8	Day 5 to 9/11
Day 12/15	Day 12 or Day 15	Day 10/12 or later
NOTE: Day 1 is the date of first selinexor or placebo. Analysis visit and visit window may change for certain parameters depending on the data availability.		

5. STATISTICAL ANALYSIS POPULATION

5.1 Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will consist of all patients who are randomized in the study with confirmed SARS-CoV2 infection under protocol version 6.0 and above, regardless of whether or not they receive study treatment. This population will be used for primary analyses of efficacy. Patients will be analyzed in the treatment arm to which they were randomized and strata assignment at the time of randomization.

5.2 Efficacy evaluable (EE) Population

The EE population is a subset of the ITT population, consisting of patients who did not die within 24 hours of randomization, had at least one post-baseline Ordinal Scale assessment, and received at least one dose of study treatment. Patients will be analyzed in the treatment arm to which they were randomized and strata assignment at the time of randomization.

5.3 All-Treat (AT) Population

The all-treat (AT) population will consist of the subset of ITT patients who took at least one dose of study treatment on this study. Patients will be analyzed based on the actual treatment received. This population will be used for primary analyses of safety.

5.4 The Proof of Concept Population

The Proof of Concept (PoC) Population consists of all patients who are randomized in the study with confirmed SARS-CoV2 infection under protocol version 1.0 to 5.0. This is a proof-of-concept cohort and thus will be analyzed separately. Efficacy and safety endpoints will be presented for descriptive purpose. Patients will be analyzed in the treatment arm to which they were treated.

5.5 Application of Analysis Population

Unless otherwise noted, the analysis populations that will be used for summaries of each set of data points are provided in Table 5.

Table 5: Application of Populations for Summary

	ITT Population	EE Population	AT Population	PoC Population
Disposition	X			X
Baseline Characteristics				
Demographics	X	X	X	X
Medical history	X		X	X
Disease history	X		X	X
Prior/concomitant medication	X	X	X	X
Tobacco use	X	X	X	X
Drug exposure and compliance			X	X
Efficacy Endpoints				
Primary efficacy endpoint	X	X		X
Key secondary efficacy endpoints	X	X		X
Other secondary endpoints	X			X
Safety Endpoints				
TEAEs			X	X
Labs			X	X
Vital signs			X	X
ECG			X	X
CCI				

6. PATIENT SUMMARY

6.1 Patients Disposition

Patients' disposition will be tabulated by treatment arm and overall using ITT and PoC Population for the following categories:

- Number of randomized patients:
  - Number of patients received at least one dose of study treatment
  - Number of patients still on-treatment
  - Number of patients with treatment discontinuation
  - Primary reasons for treatment discontinuation

A by-patient listing of study completion information, including the reason for study withdrawal will be provided.

6.2 Demographic and Baseline Characteristics

The demographic and baseline data will be summarized by treatment arm and overall including:

- Age at screening (years)
- Age in categories
- Sex
- Race.
- Ethnicity
- Weight at baseline (kg)
- BMI at baseline (kg/m^2)
- Baseline use of concomitant therapies
- Baseline comorbidities
- Baseline comorbidities by medical history
- Smoking History
- Baseline cytokines (LDH, CRP, Ferritin)

Race will be collected wherever allowed and reported for the patients for whom it is known.

6.3 Medical/Surgical History

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) Version available. Summaries will be presented by System Organ Class (SOC) and Preferred Term (PT) with numbers and percentages by treatment arm. Each patient will be counted only once in each SOC or SOC/PT summary.

In the summary table, medical history will be sorted by alphabetic order SOC and then by decreasing frequency PT within each SOC. In cases of SOCs or PTs with equal frequencies, medical history will be sorted alphabetically.

6.4 Disease History

Patients' disease history will be summarized by treatment arm including following variables:

- Days from first COVID-19 symptoms to randomization date, calculated as (date of randomization - date of initial onset of COVID-19 symptoms + 1)
- Days from admission to hospital to randomization date, calculated as (date of randomization - date of admission to hospital + 1)
- Days from date of confirmed COVID-19 diagnosis to randomization date, calculated as (date of randomization - date of confirmed COVID-19 diagnosis + 1)

6.5 Prior and Concomitant Medications

All medications will be coded using the latest WHO Drug Dictionary version available.

Prior medications are defined as those medications started prior to the administration of study treatment. Concomitant medications are defined as those medications taken after first dose of study treatment. Hence medications started before receiving study treatment but continuing after will be considered as both prior and concomitant medications.

Prior and concomitant medications will be summarized with numbers and percentages by ATC level 2 (therapeutic level), ATC level 4 (generic level) and standardized medication name separately. A patient who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification. The summary tables will be sorted by alphabetic order ATC levels and standard medication names.

6.6 Protocol Deviations

Protocol deviations will be recorded by the site staff separately from the clinical database. They may also be identified through programmable checks of the data.

A by-patient listing for all major protocol deviations will be provided.

6.7 Extent of Study Treatment Exposure and Compliance

6.7.1 Extent of Study Treatment Exposure

The extent of exposure for the study treatment will be assessed by treatment arm using the following variables:

- Duration (weeks) of exposure defined as (date of last study treatment - date of first study treatment + 1)
- Duration of exposure in category (<=1 week, (1, 2] weeks, (2, 3] weeks, (3, 4] weeks)
- Total dose received (mg) defined as sum of doses received
- Average dose received (mg/week) defined as total dose received/duration of exposure
- Number and percentage of patients with dose reduced w/wo dose delayed
- Number and percentage of patients with dose delayed w/wo dose reduced
- Number and percentage of patients with concurrent dose reduced and delayed
- Number and percentage of patients with dose held
- Number and percentage of patients with missed dose

6.7.2 Treatment Compliance

Treatment compliance (%) will be summarized by treatment arm, calculated as

$$\frac{\textbf{total number of doses taken}}{\textbf{Total number of doses scheduled}} \times \mathbf{100}.$$

Note that the number of scheduled doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

The number and percentage of patients with study treatment compliance ≥70% will be provided.

7. EFFICACY ANALYSES

Efficacy analyses will be primarily performed in ITT population. For primary and key secondary endpoints, efficacy analyses using the EE population will be considered as supportive for the corresponding analyses in the ITT population. Efficacy analyses in PoC population will be descriptive in nature.

Please refer to Table 6 below for efficacy endpoints and the corresponding definitions.

Table 6: Efficacy Endpoints and Definitions

Endpoint	Definition
Primary Endpoint	
Day 14 Ordinal Scale improvement (OSI2-14)	Proportion of patients with at least a 2 points improvement (increase) in the Ordinal Scale by Day 14. Baseline score is defined as the last score measured before first dosing. The improvement is assessed between the baseline score and the latest score on or before Day 14, End of study (EoS) date, or database cut date, whichever occurs first.
Key Secondary Endpoints	
Time to an improvement of 2 points using Ordinal Scale (TTCI-2)	The time from randomization to an improvement of 2 points on the Ordinal Scale. For patients who didn't achieve clinical improvement of 2 points, • If no death event by Day 28, they will be censored on the last contact date, on or before Day 28, EoS date, or database cut date, whichever occurs first. If they died by Day 28, they will be censored on Day 28.
Overall death rate on Day 28 (DR-28)	Proportion of patients died on or before Day 28.
Rate of mechanical ventilation (RMV)	Proportion of patients who ever used invasive mechanical ventilation or ECMO during the hospital stay.
Time to mechanical ventilation (TTMV)	Time to the first use of mechanical ventilation. For patients who never used mechanical ventilator, the censoring date is defined as the death date or last contact date (if no death), on or before EoS or database cut date, whichever occurs first.

Additional Secondary Endpoints	
Time to recovery (TTR)	Time to improvement from baseline score of 3 to ≥4 or from a baseline score of 4 to ≥5 by Day 28. For patients who didn't achieve recovery, the censoring rule will be the same as that in TTCI-2.
Day 7 Ordinal Scale 2 points improvement (OSI2-7)	Proportion of patients with at least a 2 points improvement (increase) in the Ordinal Scale from baseline to Day 7. The improvement is assessed between the baseline score and the latest score on or before Day 7, End of study (EoS) date, or database cut date, whichever occurs first.
Day 7 Ordinal Scale 1 point improvement (OSI1-7)	Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 7. The improvement is assessed the same as in OSI2-7.
Day 14 Ordinal Scale 1 point improvement (OSI1-14)	Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 14. The improvement is assessed the same as in OSI2-14.
Time to an improvement of 1 point on the Ordinal Score (TTCI-1)	The time from randomization to an improvement of 1 point on the Ordinal Scale. For patients who didn't achieve clinical improvement of 1 point, the censoring rule will be the same as that in TTCI-2.
Overall survival (OS)	Time since randomization to death date, or the last contact date with patient status being alive, on or before EoS or database cut date, whichever occurs first.
Overall death rate on Day 14 (DR-14)	Proportion of patients died on or before Day 14.
Rate of ICU admission	Proportion of patients with ICU admission.
Length of hospitalization	Length of hospital stay defined as cumulative length of hospital stay.
Length of ICU stay	Cumulative length of ICU stay.
Duration of mechanical ventilation	Cumulative number of days with invasive mechanical ventilation or ECMO

PaO2:FiO2 and/or oxygenation index over time	PaO2:FiO2 and/or oxygenation index over time. Will be summarized by visit using descriptive statistics.

7.1 Analyses of Primary Efficacy Endpoint

The difference in OSI2-14 rates between treatment arms will be calculated with a 95% confidence interval (CI). Comparison between 2 treatment arms will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. The CMH estimate of the odds ratio and its 95% CI and the p-value for testing the treatment difference will be reported.

7.1.1 Sensitivity Analyses

In a sensitivity analysis for OSI2-14, the assessment of 2 points improvement will be conducted with the baseline score defined as the last score before first dosing, or a lower score within 24 hours of randomization, whichever is lower.

The classification of whether a score can be considered as within 24 hours of randomization will be determined based on the date and time of randomization and score assessment. If there is partial date/time that make it impossible to determine whether the difference is within 24 hours, to be conservative, the score will be considered to be outside the 24-hour window.

Specifically,

- If the date of lower score is missing, it will be categorized as “outside 24 hours”.
- If the date of lower score is not missing, but hour is missing:
  - It will be categorized as “within 24 hours” if the lower score is measured on the same day of randomization.
  - It will be categorized as “outside 24 hours” if the lower score is measured on subsequent day of randomization.
- If both date and hour are not missing, but minute is missing:
  - It will be categorized as “within 24 hours” if lower score is on same day or subsequent day of randomization and hour is earlier than the hour in randomization time.

It will be categorized as “outside 24 hours” if lower score is on subsequent day of randomization and hour is the same or later than the hour in randomization time.

In the ITT population, the first approximately 50 patients were randomized with an allocation ratio of 2:1, the other patients in the ITT population will be randomized with an allocation ratio of 1:1. The switch of allocation ratio was due to an administrative reason and independent of patient characteristics and thus is not expected to cause any confounding bias. In a sensitivity analysis for OSI2-14, the CMH test will be conducted

stratifying by the randomization stratification factors and the period for the allocation ratio to assess robustness of results.

7.1.2 Subgroup Analyses

The following sub-group analyses will be conducted for OSI2-14 and TTCI-2.

- By age (≤70 vs. > 70)
- Among patients with immune compromised, have hypertension, or have pulmonary disease (smoking history or moderate to severe chronic obstructive pulmonary disease [COPD)], cardiac disease
- By baseline use of concomitant therapies
- By high-risk comorbidities (0 vs 1 vs ≥2)
- By race.

7.2 Analyses of Secondary Efficacy Endpoints

7.2.1 Analyses of Key Secondary Efficacy Endpoints

If the primary endpoint, OSI2-14, is significant in ITT population, the following key secondary endpoints in ITT population will be sequentially tested in the order listed below. If any null hypothesis is not rejected in this sequence of tests, formal sequential testing will be stopped and the analyses of any endpoints thereafter will be nominal only.

- Time to clinical improvement (TTCI-2)
- Overall Death rate on Day 28 (DR-28)
- Rate of mechanical ventilation (RMV)
- Time to mechanical ventilation (TTMV)

For binary endpoints (DR-28, RMV), the difference in rates between treatment arms will be calculated with a 95% confidence interval (CI). Comparison between 2 treatment arms will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. The CMH estimate of the odds ratio and its 95% CI and the p-value for testing the treatment difference will be reported.

For time to event endpoints (TTCI-2, TTMV), the number and percentage of patients with the corresponding events will be reported. Median event times with 95% CIs will be estimated by Kaplan-Meier (KM) method for each treatment arm. KM curves by treatment arms will be provided.

The following analysis stratified on randomization strata will be performed:

- Log-rank test stratified to compare the event times between treatment arms

- Hazard ratios of treatment effect with 95% CI estimated by Cox proportional hazards model with Efron's method of tie handling

Non-stratified log rank test and Cox proportional hazards model will be performed as sensitivity analyses.

The Kolmogorov-type Supremum test will be conducted to assess the validity of the proportion hazards assumption in all fitted Cox proportional hazards models. If there is evidence for a violation of the proportional hazards assumption, interaction terms between time-dependent terms and treatment variable (selinexor vs. placebo) will be added to assess time-varying treatment effects.

In sensitivity analysis for RMV, analyses will be conducted with patients who ever used one of the respiratory assistances as below:

- Non-invasive positive pressure mechanical ventilation (CPAP/BiPAP)
- High-flow nasal cannula
- Invasive mechanical ventilation
- Extracorporeal membrane oxygenation (ECMO)

For TTCI-2, sensitivity analyses will be performed in the same manner as OSI2-14.

7.2.2 Analyses of Additional Secondary Endpoints

For the additional secondary endpoints, binary endpoints and time to event endpoints will be analyzed similarly as for the key secondary endpoints, with the only exception that there will be no hypothesis testing.

For continuous endpoints (length of hospitalization, length of ICU stay, duration of mechanical ventilation), summary statistics by treatment arm will be provided including number of patients, median, mean, standard deviation, minimum, and maximum.

For duration of mechanical ventilation, sensitivity analyses will be performed in the same manner as RMV.

For PaO2:FiO2 and/or oxygenation index over time, only descriptive statistics will be provided.

7.2.2.1 Determination of the anti-inflammatory and immune effect of selinexor

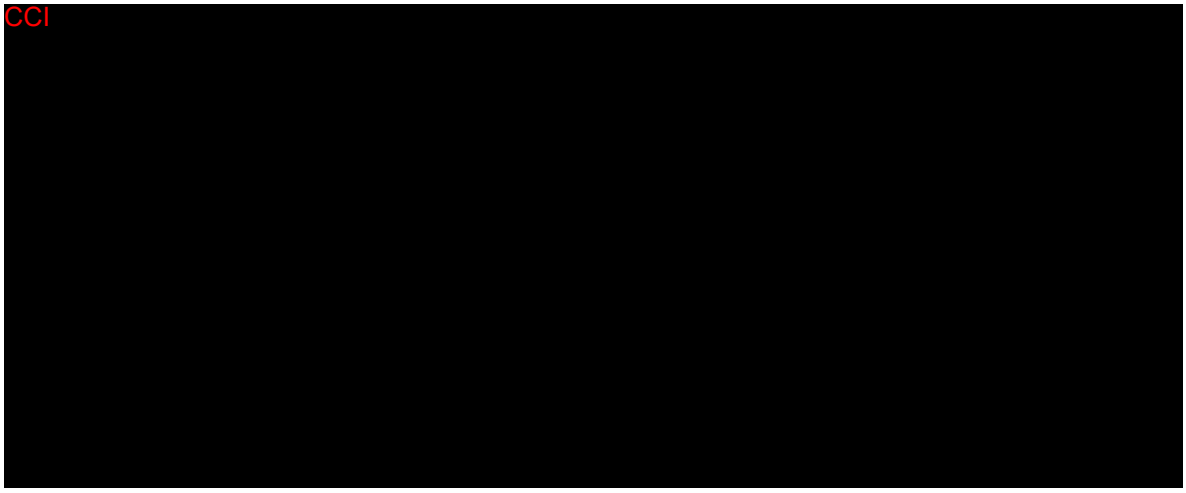
The following endpoints will be summarized by time. Change from baseline will also be summarized. The analyses will be descriptive only, no hypotheses testing will be performed.

- Reduction of C-reactive protein (CRP)
- Reduction in ferritin levels

- LDH
- Measure changes from baseline of blood plasma cytokines: IL-1β, IL-1Rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IFNγ, IP10, TNFα

7.3 Analyses of Exploratory Endpoints

CCI



8. SAFETY ANALYSES

Safety endpoints include AEs, clinical laboratory variables, vital signs, and ECGs.

Unless otherwise specified, all safety analysis will be performed by treatment arm according to the treatment the patient actually received using the AT and POC populations.

8.1 Adverse Events

Adverse events (AEs) will be coded using the most recent version of MedDRA.

The severity of all AEs will be graded according to the NCI CTCAE Grading Scale, v. 5.0. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE. For AEs not covered by CTCAE, the severity will be characterized as "mild," "moderate," "severe", "life-threatening" (corresponding to Grades 1 to 4). Handling rules for missing severity of AEs are described in Section 4.4.3.

Treatment emergent adverse events (TEAEs) are defined as those AEs that develop or worsen after the first dose of study treatment and up to 30 days beyond the last dose of study treatment. Additionally, any AEs that occurred 30 days after the last dose of study treatment will also be considered as TEAE, if assessed by the Investigator as related to study treatment.

AEs are classified as related or not related to study treatment. Any AEs with missing or unknown relationship will be considered as related to study treatment.

All summaries of AEs described in this section will be on TEAEs. All summaries will be ordered by decreasing frequency of total number of patients in overall in PT within SOC which is sorted alphabetically. In the case of equal frequency of number of patients in PTs, then summaries of AEs will be sort alphabetically.

An overall summary for AEs including number of patients who experience an TEAE will be provided:

- TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to dose reduction of study treatment
- TEAEs leading to dose interruption of study treatment
- TEAEs leading to death
- Treatment-related TEAEs
- Treatment-related serious TEAEs

- Treatment-related TEAEs leading to study treatment discontinuation
- Treatment-related TEAEs leading to dose reduction of study treatment
- Treatment-related TEAEs leading to dose interruption of study treatment
- Treatment-related TEAEs leading to death

The following types of TEAEs will be summarized by primary SOC and PT:

- All TEAEs
- All TEAEs, by causality
- All TEAEs, by maximum grade
- Grade ≥ 3 TEAEs
- Grade ≥ 3TEAEs, by causality
- TEAEs leading to study treatment discontinuation
- TEAEs leading to dose reduction of study treatment
- TEAEs leading to dose interruption of study treatment
- TEAEs leading to death
- Serious TEAEs
- Serious TEAEs, by causality

If a SOC or PT was reported more than once for a patient, the patient would only be counted once in the incidence for that SOC or PT.

For patients experiencing the same PT at multiple severities, the occurrence of the AEs with the greatest severity will be used in the analysis of incidence by severity.

For patients experiencing the same PT at multiple relationship levels, the occurrence of the AEs with the strongest relationship to study treatment will be used in the analysis of incidence by relationship to study treatment.

An overview of all death events and primary cause of death will be provided.

The following listing will be provided:

- All AEs
- Serious AEs
- AEs leading to study treatment discontinuation
- AEs leading to dose modification (reduction, interruption)
- Death

8.2 Clinical Laboratory Data

All laboratory parameters will be normalized by converting values in original units to values in SI units and classified as normal, abnormal low, or abnormal high on normal ranges supplied by the local laboratories and upon employing standardization.

Observed and change from baseline of clinical laboratory data (hematology, serum chemistry and coagulation) will be summarized at each analysis visit by treatment arm.

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. Laboratory values with CTCAE Grade ≥ 3 will be presented in a data listing. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to worst on-study relative to CTCAE classification ranges will be presented. These shift tables will include results from unscheduled visits.

8.3 Vital Signs

Observed and change from baseline of vital signs (including temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation) will be summarized at each analysis visit by treatment arm, up to ICU admission if applicable.

8.4 Electrocardiogram (ECG)

ECG will be listed only. Values of potentially clinically significant ECG (scheduled or unscheduled) will be flagged. These are defined as:

- QT, QTcF ≥ 450 msec
- QT, QTcF increase from baseline ≥ 30 msec
- PR ≤ 100 msec or PR ≥ 240 msec
- QRS ≥ 140 msec
- Heart rate ≤ 40 bmp or heart rate ≥ 120 bmp

9. PHARMACOKINETIC ANALYSES

Plasma samples will be analyzed via a validated HPLC/MS-MS method for plasma selinexor concentration. Selinexor Cmax and Ctrough data will be summarized. Selinexor concentration data might also be analyzed using a population PK modeling approach if deemed necessary. Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate Data Analysis Plan to be completed prior to database lock.

10. REFERENCES

Cui L, Hung H, Wang S. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55:853-857.
Lan K, DeMets D. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.