CLINICAL STUDY PROTOCOL

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 (XPORT-CoV-1001)

Study Number:	XPORT-CoV-1001
Study Phase:	Phase 2
Investigational Product:	Selinexor (XPOVIO®, KPT-330)
Indication:	Severe COVID-19
EudraCT Number:	TBD
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
Protocol Date and Version:	27 March 2020, Version 1.0
CONDUCT In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.	
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PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study XPORT-CoV-1001 dated 27 March 2020 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

Jatin Shah

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27 March 2020

Jatin Shah, MD
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Date

27 March 2020

Sharon Shacham, PhD
President and Chief Scientific Officer
Karyopharm Therapeutics Inc.

Date

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study XPORT-CoV-1001 dated 27 March 2020 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practice, ICH E6, and applicable FDA regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Institution

_____

Date

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LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Definition
ALT	Alanine transaminase
AST	Aspartate transaminase
AT	All-treat
CCL	Creatinine clearance
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
CMH	Cochran-Mantel-Haenszel
CRM1	Chromosome region maintenance 1
DR	Death rate
ECG	Electrocardiogram
G-CSF	Granulocyte-colony stimulating factor
IA	Interim analysis
IL	Interleukin
IκB	
INFγ	Interferon-γ
IP	Investigational product
ITT	Intent-to-treat
MCP-1	Monocyte chemoattractant protein 1
MIF-1α	Macrophage inflammatory protein 1α
MM	Multiple myeloma

MODS	Multiple organ dysfunction syndrome
NHBE	Normal human bronchial epithelial
NES	Nuclear export sequence
PFS	Progression-free survival
QoD	Every other day
RNP	Ribonucleoprotein
RSV	Respiratory syncytial virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SINE	Selective Inhibitor of Nuclear Export
TNFα	Tumor necrosis factor-α
TTCI	Time to clinical improvement
ULN	Upper limit of normal
vRNP	Viral ribonucleoprotein
XPO1	Exportin 1

SYNOPSIS

Sponsor:	**Investigational Product:**	**Study Phase:**
Karyopharm Therapeutics Inc.	Selinexor (XPOVIO®, KPT-330)	Phase 2

Title of Study: 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

Protocol Number: XPORT-CoV-1001

Study Name: XPORT-CoV-1001

Study Location:

Approximately 40 international sites are planned.

Study Rationale:

Coronavirus disease 2019 (COVID-19) is caused by the single stranded RNA virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and can be accompanied by a marked inflammatory response, which is believed to be severely determinantal to the patient and associated with multi-organ dysfunction, respiratory failure and death. Both the SARS-CoV2 lifecycle and pro-inflammatory transcription factors require functional host nuclear export mediated by exportin 1 (XPO1, also called CRM1, OMIM 602559). XPO1 was recently identified as a "hub" host protein for SARS-CoV viral propagation. Inhibition of XPO1 by the selective inhibitor of nuclear export (SINE) compound selinexor could induce both anti-viral and anti-inflammatory activities.

Selinexor (XPOVIO®, KPT-330) is a potent, oral, slowly reversible covalent SINE compound that specifically blocks the XPO1. XPO1 mediates the nuclear export of proteins and ribonucleoprotein (RNP) complexes carrying a leucine-rich nuclear export sequence (NES). Over 200 XPO1 cargo proteins have been identified including proteins with regulatory roles in the inflammatory response and many viral proteins including SARS-CoV proteins.

Selinexor received accelerated approval from the FDA in July 2019 in combination with dexamethasone as a treatment for patients with advanced multiple myeloma (MM). The approved dose of selinexor for advanced MM is 160 mg per week (80 mg PO twice weekly). Over 3000 patients with a variety of advanced cancers have received selinexor alone or in combination with other anti-neoplastic agents in clinical studies; nearly 1000 patients have received the agent commercially. The most common side effects at these high doses, namely nausea, emesis, anorexia, low sodium and low platelets are dose dependent and reversible. The dose of 20 mg three times per week (60 mg per week) used here is anticipated to be well tolerated based on two phase 1 clinical studies and to confer both anti-viral and anti-inflammatory activity as described below.

A variety of viruses produce proteins that require nuclear export to carry out their functions. SARS-CoV2 proteins, including nucleoprotein (N), protein 9b, Orf6 and potentially spike (S) and envelop (E) proteins, utilize XPO1 to properly function. Amongst >100 interacting host proteins, XPO1 and three other "hub" proteins have the highest number of functional connections with SARS-CoV proteins. Inhibition of XPO1 by the natural product XPO1 inhibitor leptomycin B results in apoptosis of the SARS-CoV-infected host cells and might prevent SARS-CoV inhibition of innate immunity as well as the marked viral-induced pro-inflammatory effects that lead to COVID-19. SINE compounds, including selinexor and the closely related analog verdinexor, block XPO1 in a fashion similar to that of

leptomycin B, are taken orally and have been shown to be tolerated in humans. Recently, selinexor was ranked 18 out of >400 drugs screened for ability to regulate SARS-CoV gene expression.

The cytokine profile observed in COVID-19 corelates with disease severity and is characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor (G-CSF), interferon-γ (INFγ) inducible protein 10, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α (MIF-1α), and tumor necrosis factor-α (TNFα) (*Lancet.* 2020; 395: 497-506). In 150 cases in Wuhan, China, independent predictors of fatality included elevated IL-6 levels ($p<0・0001$) (Ruan et al, 2020).

Host cell factors are required for the replication of all viruses. However, pharmacological manipulation of host cell factors, as a means of inhibiting viral replication, has not yet been realized. Preclinical data demonstrate that verdinexor and other SINE compounds have activity against >20 viruses, including the single stranded RNA viruses respiratory syncytial virus (RSV) and influenza, along with other common causes of respiratory infection. Specifically, verdinexor disrupts the viral replication cycle by inhibiting the interaction of viral ribonucleoproteins (vRNP) with the XPO1 nuclear export protein.

Additionally, SINE compounds reduce inflammation through inhibition of the NF-κB pathway and nuclear retention and activation of specific inhibitors of pro-inflammatory transcriptional factors such as IκB, RXRα, and PPARγ. This leads to reductions in cytokines including IL-1, IL-6 and, TNFα. This is critical for the treatment of patients with COVID-19 (and other viral infections) as the severity of disease in COVID-19 is associated with the levels of cytokine secretion in SARS-CoV infected patients.

Influenza and SARS-CoV infection induce marked host inflammatory responses, and there are predictive animal models of influenza infection. We have therefore investigated the effect of XPO1 blockade by verdinexor and related SINE compounds on infection, replication, pathology and mortality in animal and *in vitro* models of influenza. Treatment with verdinexor leads to marked nuclear accumulation of vRNP and inhibition of influenza replication. Broad-spectrum anti-influenza activity with nanomolar potency was observed with verdinexor against a variety of both influenza A and B strains in vitro. *In vivo*, oral treatment with verdinexor showed anti-influenza activity in mouse and ferret models of influenza infection. Verdinexor reduced viral burden in the lung, inhibited pro-inflammatory cytokine induction and reduced virus-associated lung pathology and pulmonary inflammation in infected animals. Verdinexor was also effective in delaying mortality and improving survival in mice challenged with a lethal infection of influenza virus, even when given 4 days *after* the initiation of infection. Given the similarities in the inflammatory processes associated with SARS-CoV and influenza viruses, these results suggest that such beneficial effects may also be observed with SINE compounds in patients with COVID-19.

Selinexor (MW 443.3) and verdinexor (MW 442.3) are closely related molecules that differ by one atom. They have similar chemical, pharmacological and pharmacokinetic properties including similar oral bioavailability. Both are potent ($Ki < 10$ nM) and highly selective inhibitors of XPO1. Both compounds form slowly reversible covalent bonds with cysteine-528 of XPO1 leading to its inactivation, and both are orally bioavailable compounds with no known drug-drug interactions. Selinexor has been most intensively studied in cell lines and preclinical models of neoplastic diseases, whereas verdinexor has been studied most intensively in viral and autoimmune disorders. Selinexor is approved for treatment in patients with advanced refractory multiple myeloma at a high dose of 160 mg per week. Lower doses of selinexor are active in a variety of other cancers and in combination with other anti-cancer agents. Existing pharmacokinetic and pharmacodynamic data support the use of selinexor in viral infections at the low dose of 20 mg three times per week. This dose of selinexor is well-tolerated and is not associated with significant cytopenias or any changes in liver function or sodium levels.

Given the urgency of the COVID-19 pandemic and drug product availability including a commercial supply of selinexor tablets, this study will be initiated with selinexor. As described above, there are no known chemical, pharmacological or toxicological distinctions between the two agents that would favor verdinexor at this time given the emergent SARS-CoV2 pandemic. Based on the pharmacokinetics of selinexor and verdinexor, low doses (e.g., 20 mg per dose) of these agents are anticipated to deliver sufficient drug to confer both anti-viral and anti-inflammatory activity in patients with viral infections, including the SARS-CoV2 virus.

Hypothesis: Oral selinexor will expedite the recovery, suppress the viral load, shorten the hospitalization and reduce morbidity and mortality in patients with severe COVID-19 compared to standard of care.

Objectives and Endpoints: Low dose oral selinexor (20 mg on QoD each week) will expedite the clinical recovery, suppress the viral load, shorten the hospitalization and reduce morbidity and mortality in patients with severe COVID-19 compared to standard of care.

Objectives and Endpoints:

Objectives	Endpoints
Primary objectives	
Time to Clinical Improvement (TTCI)	Absence of fever: oral temperature <38°C x 24 hours without antipyretics (acetaminophen) AND one of the following: – Respiratory rate ≤24/minute OR – Oxygen saturation ≥94% on room air OR – Hospital discharge
Secondary Objectives	
Mortality	All-cause mortality by Day 28 after randomization
Additional Clinical Endpoints	• Rate of and duration of mechanical ventilation • Duration of oxygen supplementation • Length of hospitalization • Length of ICU stay • Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission • Vivi Disease Score • TTCI in patients ≤70 years old • TTCI in patients >70 years old • TTCI in patients that are immune compromised, have hypertension, or have pulmonary disease (smoking history or moderate to severe COPD)

To determine the anti-inflammatory and immune effects of selinexor	• Effects on C-reactive protein (CRP) levels • Effects on ferritin levels • Effects on lactate dehydrogenase (LDH)
To assess safety and tolerability of selinexor [time frame: up to 28 days]	• Listing and documentation of frequency and severity of adverse effects

Exploratory Data (Optional)

- Measure serum TNFα, IL-1β, IL-2, IL-6, IL-7, IL-10, G-CSF, IP10, MCP-1, MIF-1α, and other cytokine expression levels before and after treatment (where available locally)
- CD4+ and CD8+ T-lymphocytes and natural killer (NK) cell count changes from baseline to end of treatment (where available locally)
- Anti-viral effects of selinexor determined by viral load changes in nasopharyngeal swab (where available locally)
- Loss of antigen positivity if available (ie, lack of high-level shedding)
- Reduction in fibrinogen levels (where available locally)
- Troponin, BNP (where available locally)
- D-Dimer (where available locally)
- CPK (where available locally)

Overall 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 well and clinically benefitting, dosing can continue for additional 2 weeks on Days 15, 17, 19, 22, 24, 26.

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

The enrollment will be stratified by:

a. Region

b. Use of concomitant therapies: an anti-viral (e.g. remdesivir) or an anti-inflammatory (e.g. hydroxychloroquine, biologics targeting e.g. IL-6 or IL-1, or both anti-viral and anti-inflammatory therapies or neither. Note: acetaminophen and NSAIDs will not constitute anti-inflammatory agents for the purposes of stratification.

Number of Patients (planned):

Approximately 230 patients will be randomized to selinexor or placebo in 1:1 ratio

Study Population: Patients have to fulfill criteria to be eligible for enrollment in the study

Eligible patients are adults ≥18 years of age admitted to the hospital with laboratory suspected and subsequently confirmed or confirmed SARS-CoV2 infection. All patients, their proxies or legal guardian must provide signed written or verbal informed consent.

Guidance for verbal consent documentation:

a. In a COVID-19 clinical trial, informed consent may be verbal in the presence of another hospital employee and/or a patient representative. In this case informed consent will be documented in the patient's chart and informed consent will be obtained per usual practice when the patient or patient's representative is able to provide after contamination concerns are no longer an issue.

b. In a COVID-19 clinical trial, if a patient is in an emergency situation and consent is not able to be obtained, consent may be obtained from a proxy on behalf of the patient or if not available consent may be deferred until the patient or their representative is able to give consent, if permitted under local law.

Inclusion Criteria:

1. Age ≥18 years
2. Clinically suspected and subsequently confirmed; or laboratory diagnosis confirming patient is positive for SARS-CoV2 nucleic acid by RT-PCR (by local labs)
3. Currently hospitalized and consented within the first 48 hours of hospitalization
4. Informed consent provided as above
5. Has symptoms of severe COVID-19 as demonstrated by:
   a. Respiratory rate ≥24 breaths/minute OR
   b. Pulse Oxygen Saturation (SpO_2) ≤94% without oxygen supplementation, OR
   c. PaO_2/FiO_2 (fraction of inspired oxygen) ≤300 mm Hg
6. Concurrent anti-virals and/or anti-inflammatory agents (e.g., biologics, hydroxychloroquine) are permitted at baseline for patients entering the study
7. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 1 week following the last dose of study treatment. Highly effective methods of contraception are listed in Section 8.3.1.

Exclusion Criteria:

1. Evidence of critical COVID-19 based on:
   a. Mechanical ventilation (invasive or non-invasive) or ECMO or hemofiltration required
   b. Shock
2. In the opinion of the investigator, unlikely to survive for at least 48 hours from screening or anticipate mechanical ventilation within 48 hours
3. Inadequate renal and liver function as indicated by the following labs:
   a. Creatinine clearance (CCL) <20 mL/min
   b. Aspartate transaminase (AST) or alanine transaminase (ALT) >5 x upper limit of normal (ULN)
4. Unable to take oral medication

Study Treatment/Treatment Groups, Dose, and Mode of Administration:

Oral 20 mg selinexor or placebo administered on Days 1, 3, 5, 8, 10, 12. If the patient is tolerating therapy well and clinically benefitting in the opinion of the treating physician, dosing can continue for additional 2 weeks on Days 15, 17, 19, 22, 24, 26.

Duration of Treatment and Follow-up:

Patients will remain on therapy for up to 14 days (or 28 days based on treating physician discretion)

Statistical Methods:

Sample Size Calculation and Statistical Power:

The total number of clinical improvement (including discharged from hospital) events required is 198, in order to achieve 80% power with a log rank test at a 1-sided significance level of 0.025 to detect a median time to clinical improvement of 15 days for the placebo arm versus 10 days for selinexor arm, resulting in a hazard ratio of 0.667, using a 1:1 randomization. With an estimated death rate of 4% and 10% drop off rate across two arms, 230 patients will be randomized.

There will be two interim analyses (IA) and one final analysis for the primary endpoint. The first interim analysis will occur after the 60^{th} event occurs. This IA is for futility only. The futility stopping boundary is Z>0.487, which is calculated using the Lan DeMets alpha spending function with the O'Brien-Fleming type of boundary. The second interim analysis happens when the 99th event occurs, efficacy boundary is Z< -2.963 and futility boundary is Z>-0.493.

If the trial is not stopped at the IA, enrollment will continue until approximately 230 patients are enrolled, the final analysis will happen when the 198th event occurs, efficacy boundary is Z<-1.937.

Analysis Populations:

The intent-to-treat (ITT) population will consist of all patients who are randomized in the study with confirmed SARS-CoV2 infection, regardless of whether or not they receive study treatment.

The all-treat (AT) population will consist of all patients who took at least one dose of study treatment on this study and have confirmed SARS-CoV2 infection.

Efficacy Analyses:

The analysis of TTCI will be performed by treatment arm based on a log-rank test. The median TTCI will be estimated with a 95% CI for each treatment arm using the Kaplan-Meier method. Hazard ratios with the associated 95% CI will be estimated by a stratified Cox proportional hazards model, using Efron's method of tie handling, with treatment as the factor. The strata will be the same stratification factors used for randomization.

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

Efficacy analyses will be performed using the ITT population.

Safety Analyses:

Safety analyses will be based on the reported AEs and other safety information, such as 12-lead electrocardiogram (ECG), clinical laboratory assessments including hematology, serum chemistry, vital signs and physical examination.

Safety analyses will be performed using the AT population.

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Activity/Assessment	Screening	Dosing Period						Extended Dosing		End-of-Study	Hospital discharge
	D -2 to -1	D1 1 day	D3 ±2 day	D5 ±2 day	D8 ±2 day	D10 ±2 day	D12 ±2 day	D 15 ±2 day	D22 ±2 day	D14/D28[a]	
Informed Consent[b]	X										
Inclusion/Exclusion	X										
Demographics	X										
Medical history	X										
Vital signs[c]	X	Twice daily during Hospital Stay									
Complete Physical Exam	X										X
Pregnancy testing	X										
Vivi Disease Score	X	Daily during Hospital Stay									
12-lead ECG	X										X
CBC with differential	X	X	X	X	X	X	X	X	X		X
Complete serum chemistry	X	X			X			X	X		X
C-reactive protein, Ferritin, LDH	X	X[d]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]		
Fibrinogen, Troponin, BNP, D-Dimer, CPK, IL-6[e]	X	X[c]		X[c]	X[c]		X[c]	X[c]			
Viral Load (Optional)	X	X		X	X		X	X			
Cells for Leukocyte Phenotyping (Optional)	X	X			X		X[f]	X[d]			
Selinexor or Placebo		X	X	X	X	X	X	(X)	(X)		
Adverse Events (any)	X	Recorded Throughout								X	
Concomitant Medications	X	Recorded Throughout								X	
Survival Follow-up										X	

[a] Patients will remain on therapy for up to 14 days (or 28 days based on treating physician discretion)
[b] Refer to section 10.1 for Informed Consent
[c] Vital signs include respiratory rate, temperature and oxygen saturation
[d] As long as patient is hospitalized
[e] Optional if locally available:
[f] Day 12 or Day 15

Table 2: Schedule of Assessment Post-Discharge Period for Outpatients Only

Activity/Assessment[a]	**D 8 ±2 day**	**D 15 ±2 day**	**D22 ±2 day**
Follow-up Call	X	X	X
Adverse Event	X	X	X
Study Drug Administration	D 15, 17, 19, 22, 24, 26		
CBC with differential[b]		X	X

[a] Sponsor Risk Management Plan for Conduct of Clinical Trials outlines procedures to be conducted during the COVID-19 pandemic.
[b] CBC is optional and only if feasible

1. INTRODUCTION

1.1. Study Rationale

Novel coronavirus disease (COVID-19) is caused by the single stranded RNA virus SARS-CoV2. The viral lifecycle requires interaction with >100 host proteins including exportin 1 (XPO1, also called CRM1). Host inflammatory response to the virus can be marked, and poor outcomes are associated with high levels of pro-inflammatory cytokines. Selinexor, and the related compound verdinexor, are highly selective and potent oral inhibitor of XPO1. These SINE compounds have been shown block the interactions of several SARS-CoV and CoV2 proteins with XPO1, and separately to reduce pro-inflammatory cytokine levels through anti-inflammatory transcriptional signaling.

Dosing verdinexor with a delay of up to 4 days in an influenza model was superior to initiation early in infection, which aligns well with the understood incubation period of the novel coronavirus. Verdinexor demonstrated activity against over 20 viruses, including respiratory syncytial virus (RSV), influenza, and other common causes of viral respiratory infection.

Selinexor (MW 443.3) and verdinexor (MW 442.3) are closely related molecules that differ by one atom. They have similar chemical, pharmacological and pharmacokinetic properties including oral bioavailability. Both are potent (Ki < 10 nM) and highly selective inhibitors of XPO1 with no known drug-drug interactions. Selinexor is approved in the U.S. in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) under the brand name XPOVIO® at doses of 160 mg per week (80 mg twice weekly). In this Clinical Trail selinexor will be dosed at 20 mg three times per week (60 mg per week total). This selinexor dose is anticipated to be well tolerated without significant cytopenias and to induce both anti-viral and anti-inflammatory activities.

1.2. Background on COVID-19

In December 2019, a novel coronavirus (subsequently named SARS-CoV2) was detected in 3 patients with pneumonia connected to the cluster of acute respiratory illness cases from Wuhan, China. By the end of February 2020, multiple countries were experiencing sustained local transmission and is now a world-wide pandemic and global health crisis.

The most commonly reported clinical symptom in laboratory-confirmed cases was fever (88%), dry cough (68%), fatigue (38%), sputum production (33%), dyspnea (19%), sore throat (14%), headache (14%) and myalgia or arthralgia (15%). Less common symptoms were diarrhea (4%) and vomiting (5%). About 80% of reported cases in China had mild to moderate disease (including non-pneumonia and pneumonia cases), 13.8% had severe disease (as defined in this protocol) and 6.1% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure). Current estimates suggest a median incubation period from 5 to 6 days for SARS-CoV2, with a range from 1 to up to 14 days. A recent modelling study confirmed that it remains prudent to consider the incubation period of up to 14 days.

Robust estimates for final case fatality risk for COVID-19 are still lacking and biased due to incomplete outcome data and the fact that initial detections were of mostly severe cases in most settings. Based on a large dataset from cases in China, the overall case fatality risk (CFR) among laboratory-confirmed cases

is currently ~0.7% for patients with symptom onset after 1 February 2020. The highest CFR among people occurs over 80 years of age (4-15%) Add reference from Synopsis.

1.2.1. Viral shedding and Transmission

Over the course of the infection, the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms and it can persist for 7-12 days in moderate cases and up to 2 weeks in severe cases. In feces, viral RNA has been detected from day 5 after onset and up to 4 to 5 weeks in moderate cases. The virus has been detected also in whole blood, serum, saliva and urine. Prolonged viral RNA shedding has been reported from nasopharyngeal swabs, up to 37 days among adult patients and in feces, for more than one month after infection in pediatric patients. It should be noted that viral RNA shedding does not directly equate with infectivity.

1.2.2. Cytokine Levels and Outcomes

Cytokine levels are associated with COVID-19 severity, characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor (G-CSF), interferon-γ (INFγ) inducible protein 10, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α, (MIF-1α) and tumor necrosis factor-α (TNFα) (Huang 2020).

Predictors of fatality of 150 confirmed COVID-19 cases in Wuhan included elevated IL-6 levels ($p<0{\cdot}0001$) (Ruan 2020).

1.3. Selinexor

Selinexor (XPOVIO, KPT-330) is a small molecule, oral, first-in-class, potent selective inhibitor of XPO1-mediated nuclear export (SINE). It has received accelerated approval from the FDA in July 2019 in combination with dexamethasone as a treatment for patients with advanced multiple myeloma (MM). The approved dose of selinexor is 80 mg po twice weekly (total 160 mg per week). More than 3000 patients with advanced cancers have received selinexor alone or in combination with other anti-neoplastic agents in clinical studies, and ~1000 additional patients have received the agent in the commercial setting. The most common side effects at these high doses, namely nausea, emesis, anorexia, low sodium and low platelets are dose dependent and reversible. The dose of 20 mg three times per week (60 mg per week) used here is anticipated to be well tolerated based on two phase 1 clinical studies and to confer both anti-viral and anti-inflammatory activity as described below.

Selinexor (MW 443.3) and verdinexor (MW 442.3) are closely related molecules that differ by one atom. They have similar chemical, pharmacological and pharmacokinetic properties. Both are potent ($Ki < 10$ nM) and highly selective inhibitors of XPO1. Both compounds form slowly reversible covalent bonds with cysteine-528 of XPO1 leading to its inactivation, and both are orally bioavailable compounds with no known drug-drug interactions. Preclinically, selinexor has been most intensively studied in cell lines and models of neoplastic diseases, whereas verdinexor has been studied most intensively in viral and autoimmune disorders.

Over 200 XPO1 cargo proteins have been identified including proteins with regulatory roles in inflammatory response and many viral proteins including severe acute respiratory syndrome coronavirus (SARS-CoV2) proteins.

A variety of viruses produce proteins that require nuclear export to carry out their functions. SARS-CoV2, including nucleoprotein (N), protein 9b, Orf6, and potentially spike (S) and envelop (E) proteins, utilize XPO1 to properly function. XPO1 and three other "hub" proteins have the highest number of functional connections with SARS-CoV proteins. Inhibition of XPO1 by the natural product XPO1 inhibitor leptomycin B results in apoptosis of the SARS-CoV-infected host cells and might prevent SARS-CoV inhibition of innate immunity as well as the marked viral-induced pro-inflammatory effects that lead to COVID-19. SINE compounds, including selinexor and the closely related analog verdinexor, block XPO1 in a fashion similar to that of leptomycin B, are taken orally and have been shown to be tolerated in humans. Recently, selinexor was ranked 18 out of 400 drugs screened for ability to regulate SARS-CoV gene expression.

Host cell factors are required for the replication of all viruses. However, pharmacological manipulation of host cell factors, as a means of inhibiting viral replication, has not yet been realized. Preclinical data demonstrate that verdinexor and other SINE compounds have activity against >20 viruses, including respiratory syncytial virus (RSV), influenza and other common causes of respiratory infection. Specifically, verdinexor disrupts the viral replication cycle by inhibiting the interaction of viral ribonucleoproteins (vRNP) with the XPO1 nuclear export protein.

Additionally, all SINEs inhibit cytokine release including IL-1, IL-6 and TNFα. They also reduce inflammation through inhibition of the NF-κB pathway and nuclear retention and activation of specific inhibitors of pro-inflammatory transcriptional factors such as IκB, RXRα, and PPARγ. This is critical for the treatment of patients with COVID-19 (and other viruses) as the severity of disease in COVID-19 is associated with the levels of cytokine secretion in SARS-CoV infected patients.

Influenza and SARS-CoV infections induce marked host inflammatory responses, and there are animal models of influenza infection available. We have therefore investigated the effect of XPO1 blockade by verdinexor and related SINE compounds on infection, replication, pathology and mortality in animal and *in vitro* models of influenza. Treatment with verdinexor leads to marked nuclear accumulation of vRNP and inhibition of influenza replication. Broad-spectrum anti-influenza activity with nanomolar potency was observed with verdinexor against a variety of both influenza A and B strains in vitro. Moreover, verdinexor exhibited anti-influenza activity *in vitro* in a model of viral replication in normal human bronchial epithelial (NHBE) cells grown in a liquid-air interface, which is a model that mimics infection of the respiratory airways in humans. *In vivo*, oral treatment with verdinexor at 10-20 mg/kg showed anti-influenza activity in mouse and ferret models of influenza infection. Verdinexor reduced viral burden in the lung, inhibited pro-inflammatory cytokine induction and reduced virus-associated lung pathology and pulmonary inflammation in infected animals. Verdinexor was also effective in delaying mortality and improving survival in mice challenged with a lethal infection of influenza virus, even when given 4 days after the initiation of infection. Given the similarities in the inflammatory processes associated with SARS-CoV and influenza viruses, these results suggest that such beneficial effects may also be observed in patients with COVID-19.

Given the urgency of the COVID-19 pandemic and drug product availability including a commercial supply of selinexor tablets, this study will be initiated with selinexor rather than verdinexor. As described above, there are no known chemical, pharmacological or toxicological distinctions between the two agents that would favor verdinexor at this time given the emergent SARS-CoV2 pandemic. Based on the pharmacokinetics of selinexor and verdinexor, low doses (e.g., 20 mg per dose) of these agents are anticipated to deliver sufficient drug to confer both anti-viral and anti-inflammatory activity in patients with viral infections, including the SARS-CoV2 virus.

Hypothesis: Low dose oral selinexor (20 mg on QoD each week) will expedite the recovery, suppress the viral load, shorten hospitalization and reduce mortality in patients with severe COVID-19 compared to standard of care.

1.4. Benefit/Risk Assessment

Blockade of XPO1 has shown anti-SARS-CoV2 activity in vitro and anti-viral effects in animal models as well as in influenza models. Severe influenza is associated with a pro-inflammatory cytokine profile similar to severe COVID-19. Based on preclinical studies, inhibition of XPO1 is anticipated to confer both anti-SARS-CoV2 and anti-inflammatory activity at relatively low doses of selinexor to be used in this study.

Higher doses of selinexor (160 mg per week) approved for use in the treatment of advanced RRMM are associated with dose-dependent and generally reversible nausea, fatigue, emesis, anorexia, low sodium and thrombocytopenia. The lower doses of selinexor used here (60 mg per week) are expected to achieve the relevant pharmacological concentrations. In addition, this dose of selinexor is well tolerated and is not associated with significant cytopenias or any changes in liver function or sodium levels. There are no known clinically significant drug-drug interactions with selinexor, nor is its use associated with opportunistic infections. The protocol allows concurrent use of other investigational anti-viral and/or anti-inflammatory agents.

Therefore, based on the available data, we believe that the opportunity to confer both anti-viral and anti-inflammatory activity with a novel agent targeting a host protein warrants provides a positive risk /benefit assessment in the treatment of severe COVID-19.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary objectives	
Time to Clinical Improvement (TTCI)	Absence of fever, oral temperature <38°C x 24 hours without antipyretics (acetaminophen) AND one of the following: – Respiratory rate ≤24/minute OR – Oxygen saturation >94% on room air OR – Hospital discharge
Secondary objectives	
Mortality	All-cause mortality by D 28 after randomization
Additional Clinical Endpoints	• Rate of mechanical ventilation • Length of hospitalization • Length of ICU stay • Duration of oxygen supplementation • Duration of mechanical ventilation • Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission • Vivi Disease Score • TTCI in patients ≤70 years old • TTCI in patients >70 years old • TTCI in patients that are immune compromised, have hypertension, or have pulmonary disease (smoking history or moderate to severe COPD)
To determine the anti-inflammatory and immune effect of selinexor	• Reduction of C-reactive protein (CRP) • Reduction in ferritin levels • LDH
To assess safety and tolerability of selinexor [time frame: up to 28 days]	• Listing and documentation of frequency and severity of adverse effects
Exploratory Endpoints	

- Serum TNF-α, IL-1β, IL-2, IL-6, IL-7, IL-10, GSCF, IP10, MCP1, MIP1α, and other cytokine expression levels before and after treatment
- CD4+ and CD8+ T-lymphocytes and natural killer (NK) cells count changes from baseline to end of treatment (where available locally)
- Anti-viral effects of selinexor determined by viral load changes in nasopharyngeal swab (where available locally)
- Loss of antigen positivity if available (ie, lack of high-level shedding)
- Changes in fibrinogen levels, Troponin, BNP, D-Dimer and CPK (where available locally)

3. STUDY DESIGN

3.1. Overall Design

This is a randomized phase 2 single-blinded study of low dose selinexor versus placebo to evaluate the activity in patients with severe COVID-19. A dose of 20 mg selinexor will be administered orally on D 1, 3 and 5 of each week for up to 2 weeks. If the patient is tolerating therapy well and clinically benefitting based on treating physician discretion, dosing can continue for an additional 2 weeks on Days 15, 17, 19, 22, 24, 26.

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

The enrollment will be stratified by:

- Region
- Use of concomitant therapies: an anti-viral (e.g. remdesivir) or an anti-inflammatory (e.g. hydroxychloroquine, biologics targeting e.g. IL-6 or IL-1, or both anti-viral and anti-inflammatory therapies or neither. Note: Acetaminophen and NSAIDs will not constitute anti-inflammatory agents for the purposes of stratification.

3.2. Scientific Rationale for Study Design

COVID-19 is caused by the single stranded RNA virus SARS-CoV2 and can be accompanied by a marked inflammatory response, which is believed to be severely determinantal to the patient and associated with respiratory failure and death. Both the SARS-CoV2 lifecycle and pro-inflammatory transcription factors require functional host nuclear export mediated by XPO1. XPO1 was recently identified as a "hub" host protein for SRAS-CoV viral propagation. Inhibition of XPO1 by the SINE selinexor could induce both anti-viral and anti-inflammatory activity.

3.3. Justification for Dose

A selinexor dose of 20 mg three times per week is anticipated to deliver a C_{max} of 159 ng/mL (359 nM) and an AUC of 1551 ng*h/mL, which is anticipated to provide both anti-viral and anti-inflammatory activity. Importantly, at doses of 12 mg/m^2 (~20 mg) selinexor AUC achieves maximal XPO1 mRNA induction (which is the pharmacodynamic marker for XPO1 inhibition). Finally, marked increased in nuclear IκB (the cellular inhibitor of NF-κB) was observed in tumor biopsies from patients with advanced cancer that were treated with selinexor at doses of ≤12 mg/m^2 (~20 mg). While the serum half-life of the agent is ~7 hours and no accumulation is anticipated with this regimen, as a slowly reversible inhibitor of XPO1, the pharmacodynamic half-life of selinexor is ~48 hours. This dose of selinexor is anticipated to induce both anti-viral and anti-inflammatory activity based on animal models with verdinexor, cell based anti-inflammatory models and pharmacodynamics data from patients with advanced cancers.

3.4. End of Study Definition

A patient will be considered having completed the study if he/she has completed up to 14 days of therapy (or 28 days per treating physician's discretion) or died.

4. STUDY POPULATION

Eligible patients are adults ≥18 years of age, admitted to the hospital, with clinically suspected and subsequently confirmed or laboratory confirmed SARS-CoV2 infection. All patients, their proxies or legal guardians must provide signed written or verbal informed consent.

4.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

1. Age ≥18 years
2. Clinically suspected and subsequently confirmed; or laboratory diagnosis confirming patient is positive for SARS-CoV2 nucleic acid by RT-PCR (by local labs)
3. Currently hospitalized and consented within the first 48 hours of hospitalization
4. Informed consent provided as above
5. Has symptoms of severe COVID-19 as demonstrated by:
    a. Respiratory rate ≥24 breaths/minute OR
    b. Pulse Oxygen Saturation (SpO_2) ≤94% without oxygen inhalation, OR
    c. PaO_2/FiO_2 (fraction of inspired oxygen) ≤300 mm Hg
6. Concurrent anti-virals and/or anti-inflammatory agents are permitted at baseline for patients entering the study
7. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 1 week following the last dose of study treatment. Highly effective methods of contraception are listed in Section 8.3.1.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Evidence of critical COVID-19 based on:
    a. Mechanical ventilation (invasive or non-invasive) or ECMO or hemofiltration required
    b. Shock
2. In the opinion of the investigator, unlikely to survive for at least 48 hours from screening or anticipate mechanical ventilation within 48 hours
3. Inadequate renal and liver function as indicated by the following labs:
    a. Creatinine clearance (CCL) <20 mL/min
    b. Aspartate transaminase (AST) or alanine transaminase (ALT) >5 x upper limit of normal (ULN)
4. Unable to take oral medication

4.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized for treatment in the study. Minimal information is required for these patients including demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE) not related to COVID-19.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening.

4.4. Randomization

Randomization will be performed prior to dosing.

Randomization will be stratified based on the following stratification factors and will maintain the 1:1 allocation between treatment arms (selinexor vs placebo) within each of the stratification categories:

- Region
- Use of concomitant therapies
  - an anti-viral therapy (e.g., remdesivir)
  - an anti-inflammatory (e.g. biologics targeting e.g. IL-6 or IL-1, or hydroxychloroquine) therapy.
  - both anti-viral and anti-inflammatory therapies
  - neither anti-viral nor anti-inflammatory therapies

  (Note: acetaminophen or NSAIDs do not constitute anti-inflammatory agents for the purposes of stratification)

5. STUDY TREATMENT

5.1. Study Treatment Administered

Table 3 shows study treatment administered.

Table 3: Study Treatment Administered

Treatment Name	Selinexor (XPOVIO, KPT-330) / Placebo
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength	20 mg
Dosage Level	20 mg, single dose
Route of Administration	Oral

5.2. Dosing and Administration of Selinexor/Placebo

5.2.1. Labeling

Medication labels for each blister pack of selinexor and matching placebo tablets will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the kit identification number, with a space to record the patient ID number after the IMP is assigned.

5.2.2. Dispensing Directions

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment as per protocol. Study treatment will be dispensed to the patient by authorized site personnel only. Additional dispensing instructions will be provided in the Pharmacy Manual.

5.2.3. Dosing Information

Study treatment tablets should be taken orally with at least 120 mL (4 ounces) of water. Study treatment can be taken with or without food. In order to avoid contact with skin, tablets must be swallowed whole and should not be crushed.

For additional details on drug formulation, preparation, and administration, please refer to the Pharmacy Manual and the Investigator's Brochure.

5.3. Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only patients randomized in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or

automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.4. Study Treatment Compliance

Administration of study treatment will be documented at each timepoint specified in the SoA. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

5.5. Concomitant Medication

5.5.1. Prohibited/Permitted Concomitant Medications

There are no prohibited concomitant medications; all medications are permitted.

5.6. Dose Modifications

Each dose modification or treatment delay must be documented, including the respective reason. The reason for dose modification should be directly related to a selinexor-associated AE, and not due to disease symptom/sign or to other medications.

For all ≥ Grade 3 hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained.

Table 4 summarizes the selinexor dose levels; Table 5 describes supportive care and dose adjustment guidelines. Deviations from the guidelines are permitted after discussion between the Sponsor and the treating physician.

Table 4: Selinexor Dose Modification Steps for Adverse Reactions

Recommended Starting Dosage	First Reduction	Second Reduction
20 mg Days 1, 3 and 5 of each week (60 mg total per week)	20 mg Days 1 and 3 weekly	20 mg Once weekly

Table 5: Selinexor Dosage Modification for Adverse Reactions

Adverse Reaction[a]	Occurrence	Action
Hematologic Adverse Reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/mcL *with* concurrent G3 bleeding	Any	• Interrupt selinexor. • Restart selinexor when bleeding resolved at one dose level lower.

Adverse Reaction[a]	Occurrence	Action
Platelet count less than 25,000/mcL	Any	• Interrupt selinexor. • Monitor until platelet count returns to at least 50,000/mcL. • Restart selinexor at one dose level lower
Non-Hematologic Adverse Reactions		
Hyponatremia		
Sodium level 130 mmol/L or less not due to disease or fluid status	Any	• Interrupt selinexor and provide appropriate supportive care. • Monitor until sodium levels return to 130 mmol/L or higher. • Restart selinexor at the same dose.
Nausea and Vomiting		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration or malnutrition) *OR* Grade 1 or 2 vomiting (5 or fewer episodes per day)	Any	• Maintain selinexor and initiate anti-nausea medications.
Grade 3 nausea (inadequate oral caloric or fluid intake) *OR* Grade 3 or higher vomiting (6 or more episodes per day)	Any	• Interrupt selinexor. • Monitor until nausea or vomiting has resolved to Grade 2 or lower or baseline. • Initiate additional anti-nausea medications for Grade 2 or lower. • Restart selinexor at one dose level lower (see Table 2).
Diarrhea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Maintain selinexor and institute supportive care.
	2nd and subsequent	• Reduce selinexor by 1 dose level (see Table 2). • Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	• Interrupt selinexor and institute supportive care. • Monitor until diarrhea resolves to Grade 2 or lower. • Restart selinexor at 1 dose level lower (see Table 2).
Weight Loss and Anorexia		
Weight loss of 10% to less than 20% *OR* anorexia associated with significant weight loss or malnutrition not due to intensive care status	Any	• Interrupt selinexor and institute supportive care. • Monitor until weight returns to more than 90% of baseline weight. • Restart selinexor at 1 less dose per week (see Table 2).
Other Non-Hematologic Adverse Reactions		
Grade 3 or 4 (life threatening)	Any	• Interrupt selinexor. • Monitor until resolved to Grade 2 or lower, restart selinexor at 1 less dose per week (see Table 2).

a. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Only adverse reactions to selinexor should lead to dose adjustments.

6. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Treatment

In rare instances, it may be necessary for a patient to permanently discontinue study treatment. If study treatment is permanently discontinued, the patient will remain in the study to be evaluated for overall mortality. See the SoA for data to be collected at the time of discontinuation of study treatment.

6.2. Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment/withdrawal from the study and record this information on the eCRF.

The Investigator may remove a patient from study treatment for any of the following reasons:

- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Significant deviations from inclusion/exclusion criteria
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk
- Any other medically appropriate reason or significant protocol violation, in the opinion of the Investigator.

The Investigator must remove a patient from study treatment for any of the following reasons:

- Patient withdraws consent to continue study treatment

6.3. Lost to Follow up

A patient will be considered lost to follow-up if he/she unable to be contacted by the study site.

6.4. Early Termination of the Study

The study may be terminated at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. If this occurs, the Sponsor will notify IECs, IRBs, Investigators, and regulatory authorities.

7. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SOA.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained prior to signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SOA.
- Please reference the Karyopharm Risk Management Plan for Conduct of Clinical Trials During the COVID-19 Pandemic as the document may address procedures being performed as a part of this clinical trial.

7.1. Baseline Assessments

7.1.1. Demographics

Patient demographics (including date of birth, sex, race, ethnicity) will be collected.

7.1.2. Medical History

The medical history will include baseline symptoms as well as active medical conditions. Data from standard-of-care procedures will be part of the patient's medical history and may be used for study purposes.

In addition, the smoking history of the patient will be recorded.

7.2. Efficacy Assessments

Study procedures and their timing are summarized in the SOA.

7.3. Safety Assessments

Planned time points for all safety assessments are provided in the SOA.

7.3.1. Physical Examinations

The physical examination will be performed according to the standards at each institution.

Complete physical examination, including vital signs, will be performed in the screening visit and if possible, at the End of Study visit. Suspected selinexor associated symptom-directed physical exam should be performed at any time directed by the clinical need as directed by the investigator.

Vital signs will include:

- Body temperature (°C or °F)
- Systolic and diastolic blood pressure and pulse rate
- Respiratory Rate

- Oxygen Saturation

Clinically relevant findings made after the start of study treatment, which meet the definition of an AE, must be recorded on the AE eCRF.

7.3.2. Electrocardiograms

Standard 12-lead ECGs will be performed at the time points specified in the SoA.

The Investigator will interpret the ECG using 1 of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant.

The time the ECG was performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected using either Bazett's or Fredericia's formula.

7.3.3. Clinical Safety Laboratory Assessments

Clinical laboratory tests (detailed in Table 6) will be performed by the sites' local laboratories. In addition, laboratory tests will be collected and analyzed at times specified on the SoA. More frequent assessments may be performed if clinically indicated.

Table 6: Clinical Safety Laboratory Tests

Hematology		
Hemoglobin	Leukocytes (with differential)	Neutrophils
Hematocrit	Platelet count	Monocytes
Basophils	Lymphocytes	Eosinophils
Serum Chemistry		
Sodium	Creatinine	ALT
Potassium	Glucose	AST
Albumin	Calcium	Alkaline phosphatase
Bicarbonate	Phosphate	Total bilirubin
BUN/Urea	LDH	Total protein

Blood chemistry will be analyzed at each study center by a certified laboratory. The Investigator or designee will review the laboratory report after receipt of the results and assess the clinical significance of all abnormal values. Results should be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values.

At any time during the study, abnormal laboratory values which are clinically relevant (eg, require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs or require therapeutic intervention), must be documented in the eCRF.

If any abnormal laboratory value or test result constitutes a selinexor related AE, then these must be recorded on the AE eCRF. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study treatment) or baseline. Any laboratory value that remains abnormal at the End of Study visit that is considered

clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline levels. Toxicity will be assessed using the NCI CTCAE, v. 5.0.

Karyopharm must be provided with a copy of the laboratory certification and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Karyopharm must be provided with a copy of the certification and normal ranges for that laboratory.

7.3.4. Adverse Events and Serious Adverse Events

Detailed information related to the collection and reporting of AEs and SAEs in Section 8.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to study treatment or study procedures, or that caused the patient to discontinue study drug (see Section 6).

7.3.4.1. Pregnancy Testing

Pregnancy testing will be performed only for females of childbearing potential. A negative serum hCG pregnancy test must be obtained at Screening (within 2 days before study treatment administration). Pregnancy testing may be performed if clinically indicated during the study.

8. ADVERSE EVENTS

8.1.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. (See Section 8.2.1.3 for additional information about SAE reporting.)

8.1.2. Recording of Adverse Events

All AEs that begin or worsen after the patient has provided informed consent will be recorded. Those AEs that occur prior to study dosing, can be captured in the patient's baseline conditions, however if any of these AEs are considered, serious, these are to be reported both to Pharmacovigilance and documented in the eCRF AE log. For events that are considered by the Investigator to be related to the study drug, the monitoring of the AE should be continued through the end of the study, for at least 30 days following last dose of study drug (if the end of the study is within 30 days of the last dose of study drug), or until the AE has resolved.

Symptoms of COVID-19 infection are not considered AEs.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the patient non-leading questions to determine if any AEs have occurred during the study, since the last study visit. Adverse events may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

8.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (ie, are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening visit) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (considered to be severe per NCI CTCAE, v. 5.0) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 8.1.1 and/or as per the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRF.

8.1.2.2. Other Adverse Events

8.1.2.3. Adverse Event Severity

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (eg, ‘severe’ headache). This is not the same as a “serious” AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If there is not a specific NCI CTCAE grading scale for an AE, the severity will be characterized as mild, moderate, severe, or life-threatening, according to the following definitions:

- Grade 1 (mild) events are usually transient in nature and do not interfere with the patient’s daily activities.
- Grade 2 (moderate) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Grade 3 (severe) events interrupt the patient’s usual daily activities.
- Grade 4 events are those that are considered to be life-threatening.

8.1.3. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as defined below.

- Not related: These events will lack a temporal relationship of the event to the study treatment, making a causal relationship not reasonably possible. Exposure to other drugs, therapeutic interventions, or underlying conditions may provide a sufficient explanation for the event.
- Related: There is a temporal relationship of the event to the study treatment making a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

8.2. Serious Adverse Events

See Section 8.1.1 for the definition of an SAE. Please note that SAEs that occur at any time between the signing of the Informed Consent Form up to the first dose of study treatment must be reported (in addition to SAEs that occur after the first dose of study treatment).

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

8.2.1.1. Events that Do Not Meet the Definition of a Serious Adverse Event

Patients are hospitalized as part of the study. If patients are kept in hospital due to a social reason or an administrative reason after they are considered to be discharged, these events will not be considered an SAE. Any other elective hospitalizations to simplify trial treatment or trial procedures or other medical procedures are not considered SAEs

Any sudden explained or unexplained death should be reported as an SAE. Death due to COVID-19 will not be considered a SAE.

8.2.1.2. Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the time when the ICF is signed until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the designated Sponsor's SAE Report Form in addition to being recorded in the eCRF. The original SAE report form must be retained in the Investigator's site file.

All applicable sections of the SAE Report Form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the form in English.

See ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Attachment 1) for key data elements that are required for expedited reporting.

8.2.1.3. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance Department within *24 hours* of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department.

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-334-7617 (USA)
+49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported, as follow-up to the original episode, within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent. An assessment should be made at each study visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome of the event.

8.2.1.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered. All SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries.

If required by local regulations, the Investigator is responsible for notifying his/her IRB or local ethics committee of all SAEs.

8.3. Procedures for Handling Special Situations

8.3.1. Pregnancy and Breastfeeding

Note: Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed below (ie, results in a low failure rate when used

consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

Highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor's Medical Monitor of the event and record the pregnancy on the Pregnancy Form (provided by Karyopharm). The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence.

The pregnancy should be followed up to determine the outcome, including any spontaneous or voluntary termination, details of the birth, and any birth defects, congenital abnormalities, or maternal and/or newborn complications.

All pregnancies occurring within 3 months after the patient's last dose of study drug must be reported to Karyopharm, regardless of whether the patient received selinexor or other study drugs, withdraws from the study, or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g. maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 8.2.1.3).

A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a selinexor-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with selinexor-containing regimen.

8.3.2. Abuse, Misuse, Medication Errors and Overdose

All incidences of abuse, misuse, medication errors and overdose are to be reported to Karyopharm Pharmacovigilance on an SAE report form to pharmacovigilance @karyopharm.com, regardless of whether or not there is an associated AE or SAE.

8.3.2.1. Overdose

An overdose is a deliberate or accidental administration of any study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, the Investigator and Karyopharm should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be documented in the patient's medical record and in the eCRF. Information regarding the overdose is to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible.

Doses of selinexor of up to 160 mg per week (80 mg twice weekly, the approved dose in RRMM) and weekly doses of up to 100 mg have been given to patients with advanced cancers with adequate tolerability. No specific antidotes for overdose are known at this time.

8.3.2.2. Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

All occurrences of abuse, misuse, or medication error with any study treatment are to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

9. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be finalized prior to database lock. Any changes from the statistical analyses described in this document will be described in the SAP, and any deviation from the final SAP will be described in the final report.

9.1. General Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as 2-sided 95% confidence intervals (CIs), unless otherwise stated.

For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

9.1.1. Procedures for Handling Missing Data

For AEs, missing dates will not be imputed; however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

9.2. Statistical Hypotheses

9.3. Sample Size Determination

The total number of clinical improvement (including discharged from hospital) events required is 198, in order to achieve 80% power with a log rank test at a 1-sided significance level of 0.025 to detect a median time to clinical improvement of 15 days for the placebo arm versus 10 days for selinexor arm, resulting in a hazard ratio of 0.667, using a 1:1 randomization. With an estimated death rate of 4% and 10% drop off rate across two arms, approximately 230 patients will be randomized.

9.4. Populations for Analyses

The intent-to-treat (ITT) population will consist of all patients who are randomized in the study, regardless of whether or not they receive study treatment.

The all-treat (AT) population will consist of all patients who took at least one dose of study treatment on this study.

9.5. Statistical Analyses

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Efficacy Analyses

The analysis of TTCI will be performed by treatment arm based on a log-rank test. The median TTCI will be estimated with a 95% CI for each treatment arm using the Kaplan-Meier method. Hazard ratios with the associated 95% CI will be estimated by a stratified Cox proportional hazards model, using Efron's method of tie handling, with treatment as the factor. The strata will be the same stratification factors used for randomization.

The difference in death rate (DR) by 28 days between treatment arms will be calculated with a 95% confidence interval (CI). Comparison of the DRs 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.

Efficacy analyses will be performed in ITT population.

9.5.2. Safety Analyses

Safety analyses will be based on the reported AEs and other clinical information.

Safety analyses will be performed in AT population.

The safety and tolerability of selinexor will be evaluated by means of drug-related AE reports, physical examinations, and laboratory safety evaluations. The grading of the severity of the AEs will be done according to CTCAE, v.5.0. Investigators will provide their assessment as either the AE is related or not related to study drug.

Treatment-emergent AEs, SAEs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment will be summarized by cohort and in the overall safety population. Treatment-emergent AEs will be those that start or worsen on or after the first day of study treatment, through 30 days after last dose. Related AEs will be those with an Investigator determination of related to study drug.

9.6. Interim Analyses

There will be 2 interim analyses (IA) and 1 final analysis for the primary endpoint. The first interim analysis happens when the 60th event occurs. This IA is for futility only. The futility stopping boundary is $Z>0.487$, which is calculated using the Lan DeMets alpha spending function with the O'Brien-Fleming type of boundary. The second interim analysis happens when the 99th event occurs, efficacy boundary is $Z<-2.963$ and futility boundary is $Z>-0.493$.

If the trial is not stopped at IA, enrollment will continue until approximately 230 patients are enrolled, the final analysis will happen when the 198th event occurs, efficacy boundary is $Z<-1.937$.

At the interim analyses, primary efficacy outcome and selected safety outcomes will be reviewed by the Data Safety Monitoring Board (DSMB) to determine if the trial will be stopped for futility or efficacy, or continue as planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Ethical and Administrative Obligations

10.1.1. Regulatory and Ethical Considerations

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations (CFR) Title 21), and with the ethical principles that originate from the Declaration of Helsinki.

The protocol and the proposed ICF(s) must be reviewed and approved by a properly constituted IRB/IEC before study start. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Karyopharm monitors, auditors, designated agents of Karyopharm, IRBs/IECs, and regulatory authorities as required.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

10.1.2. Responsibilities of the Investigator and Good Clinical Practice

- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3. Informed Consent Process

Karyopharm will provide to Investigators, in a separate document, proposed ICFs that are considered appropriate for this study and comply with the ICH GCP guidelines and regulatory requirements. Any changes to the ICFs suggested by the Investigator must be agreed to by Karyopharm before submission to the IRB/IEC, and a copy of the approved version(s) must be provided to the Karyopharm after IRB/IEC approval.

All patients, proxies or legal guardians must provide signed written or verbal informed consent as follows:

- In a COVID-19 clinical trial, informed consent may be verbal in the presence of another hospital employee and/or a patient representative. In this case informed consent will be documented in the patient's chart and informed consent will be obtained per usual practice when the patient or patient's representative is able to provide after contamination concerns are no longer an issue.
- In a COVID-19 clinical trial, if a patient is in an emergency situation and consent is not able to be obtained, consent may be obtained from a proxy on behalf of the patient or if not available consent may be deferred until the patient or their representative is able to give consent, if permitted under local law.

Females of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Males should be informed that taking the study drug may lead to reductions in sperm counts, including marked reductions. Recovery from this may take weeks or months and may not be

complete and the effects on sperm during recovery are not known. In order to participate in the study, males must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.4. Data Collection and Management

10.4.1. Data Confidentiality

Patients will be assigned a unique identifier by the Karyopharm. Signed ICFs and patient enrollment logs must be kept strictly confidential to enable patient identification at the site.

Any patient records or datasets that are transferred to Karyopharm will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (eg, has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential patient information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

10.4.2. Data Collection

Data collection is the responsibility of the clinical study staff at the site, under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the eCRF system.

10.4.3. Site Monitoring

Before site activation, Karyopharm personnel (or designated contract research organization [CRO]) will review the protocol and applicable study documents with the Investigators and their

staff (eg, at a site initiation visit). During the study, the monitor must have access to the source documents to check the completeness of patient records, accuracy of entries on the CRFs, adherence to the protocol and to Good Clinical Practice (GCP), progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits. Remote study monitoring could be used, more details will be provided in the study-specific monitoring plan.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The Investigator must also keep the original signed ICF (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Karyopharm monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

10.4.4. Data Collection

This study will utilize electronic data capture (EDC), the designated clinical site staff will enter the data required by the protocol into the eCRF. The eCRFs will be constructed using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Clinical site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the Investigator staff.

The Investigator is responsible for assuring that the data entered into the eCRF is complete and accurate, and that entry and updates are performed in a timely manner.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

10.4.5. Database Management and Quality Control

Karyopharm personnel (or designated CRO) will review the eCRF data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study, after discrepancies and missing values have been completed and the data have been verified to be complete and accurate, the database will be declared locked.

For EDC studies, after database lock, the Investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10.5. Data Safety Monitoring Committee Responsibility

At the interim analyses, primary efficacy outcome and selected safety outcomes will be reviewed by the DSMB to determine if the trial will be stopped for futility or efficacy or continue as planned (Section 9.6). The DSMB may also meet at other times during the study as needed.

10.6. Dissemination of Clinical Study Data

Results from the study (including demographics, baseline characteristics, primary and secondary endpoints) will be posted in a publicly accessible database (such as www.clinicaltrials.gov or EudraCT) in accordance with applicable laws, regulations, and/or guidelines.

In addition, upon study completion and finalization of the clinical study report, the results of this study may be submitted for publication in a peer-reviewed journal or presented at a scientific/biomedical conference.

10.7. Source Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Karyopharm-sponsored study, each site will permit authorized representatives of Karyopharm and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

The Investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the clinical study unless Karyopharm provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

10.8. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

10.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11. REFERENCES

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.

Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 Mar 3.