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: **IND Number**	2020-001411-25 CCI
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 (Original) 05 April 2020, Version 2.0 (Amendment 1) 07 April 2020, Version 3.0 (Amendment 2 - country specific US) 09 April 2020, Version 4.0 (Amendment 3 - country specific US) 11 April 2020, Version 4.0 (Amendment 4 - Global) 15 April 2020, Version 4.0 UK (country specific United Kingdom) 18 April 2020, Version 4.0 DE (country specific Germany) 18 April 2020, Version 4.0 IL (country specific Israel) 02 May 2020, Version 5.0 (country specific US) 04 May 2020, Version 1.1 (country specific Italy) 08 May 2020, Version 6.0 (country specific US)

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.

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 08 May 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:

PPD **MD** **Date**

PPD

Karyopharm Therapeutics Inc.

PPD **PhD** **Date**

PPD

Karyopharm Therapeutics Inc.

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study XPORT-CoV-1001 dated 08 May 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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CCI [redacted]

LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation	Definition
ABG	arterial blood gas
AE	adverse event
ALT	alanine transaminase
AMI	acute myocardial infarction
AST	aspartate transaminase
AT	all-treat
ATC	Anatomical Therapeutic Chemical
AUC	area under the time-concentration curve
CCI	[redacted]
BUN	blood urea nitrogen
CAD	coronary artery disease
CrCL	creatinine clearance
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CCI	[redacted]

CRO	contract research organization
CRP	C-reactive protein
C_{trough}	trough plasma concentration
CCI [redacted]	
CRM1	chromosome region maintenance 1 (also called exportin 1)
DR	death rate
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	Electrocardiogram
EDC	electronic data capture
ECMO	extracorporeal membrane oxygenation
FDA	Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GCP	good clinical practice
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
IA	interim analysis
ICF	informed consent form
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
IκB	inhibitor of nuclear factor-kappa b (nf-κb)
INFγ	interferon-γ
IP	investigational product

ITT	intent-to-treat
LPM	liters per minute
MCP-1	monocyte chemoattractant protein 1
MIF-1α	macrophage inflammatory protein 1α
MM	multiple myeloma
MODS	multiple organ dysfunction syndrome
MW	molecular weight
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NES	nuclear export sequence
NF-κB	nuclear factor κb
NG	Nasogastric
NHBE	normal human bronchial epithelial
NSAID	nonsteroidal anti-inflammatory drugs
OSI	Ordinal Scale for Clinical Improvement
PEG	percutaneous endoscopic gastrostomy
PFS	progression-free survival
PHI	protected health information
PPARγ	peroxisome proliferator-activated receptor γ
PR	partial response
QoD	every other day
RNA	ribonucleic acid
RNP	Ribonucleoprotein
RRMM	relapsed/refractory multiple myeloma
RSV	respiratory syncytial virus

CCI	
RXRα	retinoid x receptor alpha
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV	Severe acute respiratory syndrome coronavirus
SINE	selective inhibitor of nuclear export
SoA	schedule of assessments
SoC	standard of care
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor-α
TTCI	time to clinical improvement
ULN	upper limit of normal
vRNP	viral ribonucleoprotein
WHO	World Health Organization
XPO1	exportin 1 (also called CRM1)

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 Infection

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 detrimental to the patient and associated with multi-organ dysfunction, respiratory failure and death (Lai 2020). 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 (Zhou 2020). 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 inhibits XPO1. XPO1 mediates the nuclear export of proteins and ribonucleoprotein (RNP) complexes carrying a leucine-rich nuclear export sequence (NES) (Behrens 2017). 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. In a recent study, selinexor was shown to potently inhibit SARS-CoV2 viral propagation in Vero cells with IC_{50} and IC_{90} of <10nM and 100nM, respectively.

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 (Gavriatopoulou 2020).

Selinexor was initially evaluated in two Phase 1 dose escalation studies in patients with advanced heavily pretreated hematologic (KCP- 330-001) and solid tumors (KCP- 330-002). These patients had multiple lines of prior chemotherapy and were severely immunocompromised frail patients with heavily pre-treated relapsed refractory hematologic and solid tumors. Selinexor at doses of ≤12 mg/m^2 (~20 mg) demonstrated target engagement in patients' tumor biopsies as assessed by nuclear localization of XPO1 cargoes such as IκB and FOXO1 (pre- and 2-4 weeks post-treatment biopsies) (Razak 2016; Karyopharm Data on File). Durable anti-tumor activity was observed in patients with both advanced hematological and solid tumors was observed at doses of ≤12 mg/m^2, despite the fact that these patients had advanced, heavily pretreated neoplasms that were refractory to available anti-cancer agents (Kuruvilla 2017; Garzon 2017; Razak 2016).

At a dose ≤12 mg/m^2 (~20 mg) in the first 2 weeks, the 5 most common non-hematologic adverse events (AEs) were low grade (Grade 1 and 2) nausea, decreased appetite, fatigue, vomiting and dysgeusia, that

was manageable with supportive care. Hematologic AEs included only thrombo-cytopenia, and the Grade 3 and 4 events (1 each) were observed in patients with refractory hematologic cancers (acute leukemia and MM) (Appendix 2). There were no clinically significant changes in serum chemistries. Nearly all of the adverse events were reversible and responded to supportive care. Finally, there were no clinically significant drug-drug interactions at these low doses, nor were any observed at much higher doses. Based on these results, 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 detailed in Appendix 2) 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 (Zhou 2020). 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 (Jorquera 2018). 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 ability of selinexor to inhibit SARS-CoV2 viral propagation was evaluated in vero cells using two approaches: (a) prophylactic (pre-treatment) of cells with selinexor prior to infection and (b) concurrent treatment with selinexor at the time of infection (co-incubation). Pretreatment or co-incubation of selinexor resulted in significant inhibition of viral propagation with IC_{50} of ~10 nM and the IC_{90} of ~100 nM. 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) (Huang 2020). In 150 cases in Wuhan, China, independent predictors of fatality included elevated IL-6 levels ($p<0.0001$) (Ruan 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 anti-inflammatory targets such as IκB, RXRα, and PPARγ (Tajiri 2016; Kashyap 2016; Widman 2018). This leads to reductions in cytokines including IL-1, IL-6 and, TNFα. In a model that is relavant to severe COVID-19 with respiratory insufficiency, selinexor was evaluated in a mouse model of sepsis and ARDS utilizing an intraperitoneal injection of a lethal dose of bacterial endotoxin (LPS). In this sepsis model, selinexor given via oral gavage administered 30 minutes after the lethal dose of endotoxin treatment increased survival at a dose of ≥15 mg/m^2 (Wu 2018).

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 (Perwitasari 2016). 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* (Perwitasari 2016). *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 (Perwitasari 2016). 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 (Appendix 2). 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 MM 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 + standard of care (SoC) will expedite the recovery, suppress the viral load, shorten the hospitalization and reduce morbidity and mortality in patients with severe COVID-19 compared to placebo + SoC.

Objectives and Endpoints: Low dose oral selinexor (20 mg on QoD each week) + SoC 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 placebo + SoC.

Objectives	Endpoints
Primary Objectives	
Day 14 Ordinal Scale Improvement (OSI)	Proportion of patients with at least a 2 point improvement (increase) in the Ordinal Scale from baselineto Day 14. The Ordinal Scale is an assessment of the clinical status at the first assessment on each day of hospitalization. The scale is as follows: 1. Death; 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

	3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7. Not hospitalized, limitation on activities and/or requiring home oxygen; 8. Not hospitalized, no limitations on activities.
Key Secondary Objectives	
To evaluate improvement in clinical measures across the 2 treatment arms	• Time to recovery defined as improvement from baseline score of 3 to ≥4 or from a baseline score of 4 to ≥5 • Proportion of patients with at least a 2 point improvement (increase) in the Ordinal Scale from baseline to Day 7. • Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 7 • Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 14. • Time to an improvement of 2 point using WHO Ordinal Scale Improvement (TTCI-2) • Time to clinical improvement (TTCI-1): defined as the time from randomization to an improvement of 1 point on the Ordinal Scale • Overall death rate on Day 28 • Rate of mechanical ventilation
Additional Secondary Objectives	
To evaluate improvement in additional clinical measures across the 2 treatment arms	• Overall Survival • Overall death rate on Day 14 • Rate of ICU admission • Length of hospitalization • Length of ICU stay

	• Duration of mechanical ventilation • PaO_2:FiO_2 and/or oxygenation index over time
To determine the anti-inflammatory and immune effect of selinexor	• Reduction of C-reactive protein (CRP) • Reduction in ferritin levels • LDH • Measure changes from baseline of blood plasma cytokines: IL-1β, IL-1Rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IFNγ, IP10, TNFα
To assess safety and tolerability of selinexor [time frame: up to 28 days]	• Listing and documentation of frequency and severity of adverse effects
To characterize selinexor pharmacokinetics	• Selinexor PK parameters, maximum plasma concentration (C_{max}) and trough concentration (C_{trough}), if feasible
Exploratory Endpoints	
CCI [redacted]	

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.

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

The enrollment will be stratified by:

- 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). Note: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) will not constitute anti-inflammatory agents for the purposes of stratification.
- High Risk Comorbidities: Age > 75, BMI> 30, cancer patients on chemotherapy, patients with cardiac (CAD, AMI, CHF) or pulmonary (COPD, emphysema) disease diabetes, hypertension). Stratification will be based on number of high risk comorbidities: (1 vs ≥2 vs 0)

A dose of 20-mg selinexor or matching placebo will be administered orally on Days 1, 3, and 5 of each week for up to 2 weeks. If the patient is tolerating therapy and clinically benefitting (i.e., not meeting

any of the criteria for stopping therapy listed below), dosing can continue for an additional 2 weeks (on Days 15, 17, 19, 22, 24, and 26).

Patients who achieve ANY of the following criteria will be considered as having clinical benefit for the purpose of continuing dosing for an additional 2 weeks.

1. Patients who remains hospitalized and:
    a. Has not had a selinexor-related Grade 4 AE or selinexor-related serious AE (SAE)

    AND

    b. Has not had >1 point ordinal score reduction (worsening)

    OR

    c. Has 2 point reduction (worsening) in ordinal score with a ≥20% absolute reduction in FiO2 from peak oxygen requirement
2. Patients discharged from the hospital before Day 28 must meet the following criteria in order to continue on selinexor:
    a. Platelet count >75,000/mm^3 and
    b. Neutrophil count >1,000/mm^3 and
    c. Serum sodium >130 mmol/L and
    d. No Grade ≥3 nausea or vomiting and
    e. No Grade 4 AEs considered to be related to selinexor and
    f. Improved ordinal score from baseline AND
    g. Positive SARS-CoV2 by FDA approved laboratory test at discharge

Number of Patients (planned):

Approximately 300 patients will be enrolled overall as follows:

a. ~50 patients in Protocol version ≤5.0
b. The ITT population will include 247 patients that will be enrolled in Protocol Version 6 and will be randomized to selinexor or placebo in a CCI ratio

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

Eligible patients are adults ≥18 years of age admitted to the hospital with confirmed SARS-CoV2 infection. All patients or their proxies must provide signed written or verbal informed consent. The Informed Consent Form (ICF) and the process to obtain the informed consent will comply with all local laws, regulations, and guidance.

Inclusion Criteria:

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

1. Age ≥18 years
2. Confirmed laboratory diagnosis of SARS-CoV2 by standard FDA-approved RT-PCR assay or equivalent FDA-approved testing (local labs) within 7 days of enrollment
3. Currently hospitalized
4. Informed consent

5. Has symptoms of severe COVID-19 as demonstrated by:
    a. At least 1 of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion, or symptoms of severe lower respiratory symptoms including dyspnea at rest or respiratory distress
    AND
    b. Clinical signs indicative of lower respiratory infection with COVID-19, with at least one of the following: SaO_2 <92% on room air in last 12 hours or requires ≥4 LPM oxygen by nasal canula, non-rebreather/Ventimask (or similar device) or high flow nasal canula in order to maintain SaO_2 ≥92%, PaO_2/FiO_2 <300 mm/hg. Patients with COPD or chronic lung disease must demonstrate evidence of increased oxygen needs above baseline.
6. Elevated CRP > 2 x ULN
7. Concurrent anti-viral and/or anti-inflammatory agents (e.g., biologics, hydroxychloroquine) are permitted. If in the physician's judgement, it is in the best interest of the patient to use anti-viral or anti-inflammatory treatments, these treatments are to be documented in the patient's chart and entered in the electronic case report form.

    Note: Patients who may have received plasma convalescent therapy > 48 hours prior to enrollment with no clinical improvement and who still meet criteria for severe COVID-19 may enroll. On study plasma convalescent therapy is not permitted.
8. Patient who receive plasma convalescent therapy within 48 hours may be permitted to enroll based on discussion with sponsor.Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients must use highly effective methods of contraception throughout the study and for 3 months 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. Respiratory failure (defined by endotracheal intubation and mechanical ventilation, oxygen delivered by noninvasive positive pressure ventilation, or clinical diagnosis of respiratory failure in setting of resource limitations)
    b. Septic shock (defined by investigator assessment or requires vasopressors)
    c. Multiple organ dysfunction/failure
2. In the opinion of the investigator, unlikely to survive for at least 48 hours from screening.
3. Inadequate hematologic parameters as indicated by the following labs:
    a. Patients with severe neutropenia (ANC <1000 x 10^9/L) or
    b. Thrombocytopenia (e.g., platelets <100,000 per microliter of blood)
4. Inadequate renal and liver function as indicated by the following labs:
    a. Creatinine clearance (CrCL) <20 mL/min using the formula of Cockcroft and Gault.
    b. Aspartate transaminase (AST) or alanine transaminase (ALT) > 5 x upper limit of normal
5. Hyponatremia defined as sodium less than 130 mEq/L
6. Unable to take oral medication when inform consent is obtained.
7. Patients with a legal guardian or who are incarcerated.

8. Patients taking strong CYP3A inhibitors or inducers. A list of prohibited strong CYP3A inhibitors and inducers is provided in Appendix 3.
9. Pregnant and breastfeeding women.

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

A dose of 20 mg selinexor or matching placebo will be administered orally on Days 1, 3, and 5 of each week for up to 2 weeks. If the patient is tolerating therapy and clinically benefitting, as defined below, dosing can continue for an additional 2 weeks (on Days 15, 17, 19, 22, 24, and 26).

Duration of Treatment and Follow-up:

Patients will receive study treatment for up to 14 days.

Dosing can continue for an additional 2 weeks if ANY of the following criteria are met:

1. Patients who remain hospitalized must meet the following criteria to continue selinexor therapy:
    a. has not had a selinexor-related Grade 4 Advese Event (AE) or selinexor-related Serious AE (SAE) AND
    b. has not had >1 point ordinal score reduction (worsening) OR
    c. has 2 point reduction (worsening) in ordinal score with a ≥20% absolute reduction in FiO2 from peak oxygen requirement
2. Patients discharged from the hospital before Day 28 must meet the following criteria to continue selinexor therapy:
    a. Platelet count > 75,000/mm^3 and
    b. Neutrophil count >1,000/mm^3 and
    c. Serum sodium > 130 mmol/L and
    d. No Grade ≥3 nausea or vomiting and
    e. No Grade 4 AEs related to selinexor, and
    f. Improved ordinal score from baseline AND
    g. Positive SARS-CoV2 by FDA approved laboratory test at discharge

    Note: patients discharged from the hospital who remain on selinexor must continue to have twice weekly serum chemistry and complete blood counts as long as treatment is continued.

Therapy will be stopped if any of the events defined below occur prior to 28 days:

- Patient withdraws consent to continue study treatment.
- Worsening clinical condition defined as at least 5 days of intubation/ECMO with no evidence of clinical improvement. Patients who are clinically stable based on oxygen requirements on mechanical ventilation will be permitted to remain on study.
- Grade ≥3 nausea or vomiting despite optimal antiemetic therapy.
- Progression of renal dysfunction requiring dialysis.
- Grade 4 AEs related to selinexor

Statistical Methods:

Sample Size Calculation and Statistical Power:

Approximately 247 patients CCI [redacted]

Analysis Populations:

The intent-to-treat (ITT) population will consist of all patients who are randomized in the study with confirmed SARS-CoV2 infection under protocol version 6.0 and above, regardless of whether or not they receive study treatment.

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 difference of the primary endpoint (Day 14 OSI) between treatment arms will be calculated with a 95% confidence interval (CI). Comparison of OSI rates between the 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.

Analyses of other efficacy endpoints will be specified in Section 9.4.1 and the SAP.

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 for admitted patients only

Activity/Assessment	Screening	Dosing Period										End-of-Treatment	Hospital Discharge	Safety Follow-Up / End of Study[j]
	D -2 to D1	D1 ±1 day	D3 ±1 day	D5 ±1 day	D8 ±1 day	D10 ±1 day	D12 ±1 day	D 15 ±1 day	D 19 ±1 day	D22 ±1 day	D26 ±1 day	D14/28[a]		
Informed Consent[b]	X													
Inclusion/Exclusion	X													
Demographics	X													
Medical history	X													
Disease History	X													
Vital signs[c]	X	Twice daily during Hospital Stay												
Complete Physical Exam	X												X	
Pregnancy testing (per site guideline)	X											X		
Ordinal Score[d]	X	Daily and the day after discharge											X	
12-lead ECG[e]	X	As clinically indicated												
ABG (Arterial Blood Gas)[l]	X	As clinically indicated												
CBC with differential	X	X	X	X	X		X	X	X	X	X		X	
PT. aPTT, INR	X	X	X	X	X		X	X		X	X			
Complete serum chemistry	X	X	X	X	X		X	X	X	X	X		X	
C-reactive protein, Ferritin, LDH[f]	X	X	X	X	X		X	X	X	X	X			
CCI	[redacted]													

Cells for Leukocyte Phenotyping[f]	X	X			X		X[g]	X						
Selinexor or Placebo[k]		X	X	X	X	X	X	(X)	(X)	(X)	(X)			
Blood draws for selinexor PK[h]		X	X	X										
Cytokines	X		X	X	X									
Adverse Events (any)	X	Recorded Throughout										X		X
Concomitant Medications	X	Recorded Throughout										X		
5-HT3 antagonists Ondansetron or equivalent[j]		Daily as needed												
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 It is recommended to measure SpO_2 in the same position for each patient throughout the duration of the study
d Ordinal Score (Section 7.3.2) will be assessed at first assessment of day
e For patients who had an ECG during the hospitalization, the ECG does not need to be repeated. Results of this most recent ECG should entered into the eCRF
f Required study and should be performed unless hospital SOP does not permit or if not feasible, to be performed locally as available. Once 2 negative viral assessments are documented testing can be stopped.
g Day 12 or Day 15
h Blood samples (~ 2mL) for selinexor PK will be collected at 4 ± 1 hr, 24 ± 4 hrs post selinexor dose on Day 1 and predose on Day 3 and Day 5. Details for PK sample collection and processing can be found in the Laboratory Manual.
i This visit will occur 30 (+2) days post end of treatment and may be performed as either a telephone call or an in-clinic visit. Only follow up on SAEs will be reported.
j In order to minimize nausea, all patients should receive ondansetron 8 mg or equivalent unless contraindicated, starting on Day 1 before the first dose of selinexor and continued 2-3 times daily thereafter, as needed. Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonists.
k It is recommended that patients are dosed with study drug within 12 hours of consent
l If feasible.

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

Activity/Assessment[a]	Schedule	Day 28	End of Study[b]
Follow-up Call	Weekly until day 28		X
Ordinal Score	On Day 7 and 14		
Adverse Event	Weekly until day 28		X
Study Drug Administration[c]	Dosing Days 1, 3, 5 of each week until day 28		
CBC with differential and Complete Serum Chemistry[c]	Twice weekly until 14 or day 28		
CCI			
Survival Follow-up		X	

[a] Sponsor Risk Management Plan for Conduct of Clinical Trials outlines procedures to be conducted during the COVID-19 pandemic.
[b] This visit will occur 30 (+2) days post end of treatment, and may be performed as either a telephone call or an in clinic visit. Only follow on SAEs will be reported.
[c] Only for patients who are discharged on study treatment and while on study treatment . Decision to continue beyond day 14 is per protocol guidelines

1. INTRODUCTION

1.1. Study Rationale

Novel coronavirus disease (COVID-19) is caused by the single stranded RNA virus SARS-CoV2 (Cascella 2020). 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. In a recent study, selinexor was shown to potently inhibit SARS-CoV2 viral propagation in Vero cells with IC_{50} and IC_{90} of < 10nM and 100nM respectively (see Section 1.3). 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 as efficacious as initiation early in infection, which aligns well with the understood incubation period of the novel coronavirus (Perwitasari 2016). Verdinexor demonstrated activity against over 20 viruses, including respiratory syncytial virus (RSV), influenza, and other common causes of viral respiratory infection (Jorquera 2018; Widman 2018).

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 Trial, 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%) (Huang 2020; Ruan 2020).

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 ability of selinexor to inhibit viral propagation was evaluated using two approaches: (a) prophylactic (pre-treatment) of cells with selinexor prior to infection and (b) concurrent treatment with selinexor at the time of infection (co-incubation).

CCI

CCI

Low dose selinexor: biological activity, efficacy and safety in patients with advanced cancer

Selinexor was initially evaluated in 2 Phase 1 dose escalation studies in patients with advanced heavily pretreated hematologic (KCP- 330-001) and solid tumors (KCP- 330-002). These patients had multiple lines of prior chemotherapy and were severely immunocompromised frail patients with heavily pre-treated relapsed refractory hematologic and solid tumors. Selinexor at doses of ≤12 mg/m^2 (~20 mg) demonstrated target engagement in patients' tumor biopsies as assessed by nuclear localization of XPO1 cargoes such as IκB and FOXO1 (pre- and 2-4 weeks post-treatment biopsies) (Razak 2016; Karyopharm Data on File). Durable anti-tumor activity was observed in patients with both advanced hematological and solid tumors was observed at doses of ≤12 mg/m^2, despite the fact that these patients had advanced, heavily pretreated neoplasms that were refractory to available anti-cancer agents (Kuruvilla 2017; Garzon 2017; Razak 2016).

At a dose ≤12 mg/m^2 (~20 mg) in the first 2 weeks, the 5 most common non-hematologic adverse events (AEs) were low grade (Grade 1 and 2) nausea, decreased appetite, fatigue, vomiting and dysgeusia, that was manageable with supportive care. Hematologic AEs included only thrombocytopenia, and the Grade 3 and 4 events (1 each) were observed in patients with refractory hematologic cancers (acute leukemia and myeloma) (Appendix 2). There were no clinically significant changes in serum chemistries. Nearly all of the adverse events were reversible and responded to supportive care. Finally, there were no clinically significant drug-drug interactions at these low doses, nor were any observed at much higher doses. The C_{max} with 20 mg selinexor is 159 ng/mL (359 nM). Based on these results, 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 (detailed in Appendix 2) and to confer both anti-viral and anti-inflammatory activity as described below.

Activity of Selinexor and other SINE compounds in models of Inflammation and Viral Infection

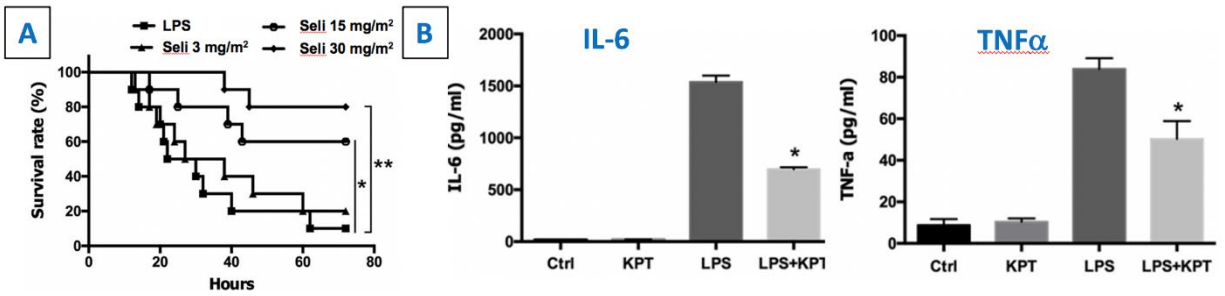
Selinexor (MW 443.3) and verdinexor (MW 442.3) are closely related molecules that differ by one atom. They have similar chemical, pharmacological and pharmacokinetic properties. Both are potent (Ki < 10 nM) and highly selective inhibitors of XPO1. Both compounds form slowly reversible covalent bonds 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 (Appendix 1).

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 (Zhou 2020).
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 (Sharma 2011; Reed 2007). XPO1 and three other "hub" proteins have the highest number of functional connections with SARS-CoV proteins (Gordon 2020). 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 analysis done by Califano et al (private communication).

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 (Widman 2018; Perwitasari 2016; Jorquera 2018).

Additionally, Selienxor and other SINEs inhibit cytokine release including IL-1, IL-6 and TNFα 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 (Tajiri 2016; Kashyap 2016; Widman 2018) In a model that is relavant to severe COVID-19 with respiratory insufficiency, selinexor was evaluated in a mouse model of sepsis and ARDS utilizing an intraperitoneal injection of a lethal dose of bacterial endotoxin (LPS). In this sepsis model, selinexor given via oral gavage administered 30 minutes after the lethal dose of endotoxin treatment increased survival at a dose of ≥15 mg/m^2 (Wu 2018; Figure 2). In addition, selinexor reduced inflammatory cytokine levels in the serum including TNFa, IL-6 and HMGB1, while reducing the numbers of macrophages and polymorpho-nuclear neutrophils in the mouse peritoneal cavity. Importantly, selinexor treatment attenuated the ARDS-like lung injury observed in this model. Details are provided in Appendix 1.

Figure 2: Sepsis Model for Selinexor.



Oral selinexor dosed 30 minutes after the induction of sepsis protected the mice and increased their survival (Figure 2A). In addition, serum levels of the proinflammatory cytokines TNFa and IL-6 at 12 h post LPS challenge were significantly lower in selinexor treatment groups (Figure 2B).

As the severity of respiratory disease in COVID-19 is associated with the levels of cytokine secretion in SARS-CoV infected patients, the observed reductions in cytokine levels in this sepsis-ARDS model, as well as the results in influenza described below, support the view that treatment of patients with COVID-19 (and other respiratory viruses) with selinexor could be beneficial.

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 (Perwitasari 2016). 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 (Perwitasari 2016).

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. There are no known clinically significant drug-drug interactions with selinexor. The protocol allows concurrent use of other investigational anti-viral and/or anti-inflammatory agents.

The highly selective and potent oral XPO1 inhibitors verdinexor and selinexor have no pharmacologically important discernable differences. XPO1 inhibitors have activity in models of sepsis/ARDS, inflammation, and influenza. In a recent study selinexor demonstrated potent activity against SARS-CoV2 (IC_{50}= ~10 nM). The adverse event profile of low dose selinexor consists of low grade, reversible and treatable symptoms (Appendix 2).

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

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

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

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.

The study has 2 arms and will evaluate selinexor 20 mg + standard of care (SoC) and placebo + SoC. As the treatment for COVID-19 is rapidly evolving, the SoC will vary over time and across regions of the world. Therefore, SoC may include antibiotics (e.g., azithromycin), anti-malarial (e.g., hydroxychloroquine), or antivirals (e.g., remdesivir), and other agents (e.g., anti-IL-6 antibodies) to be per the institution at each site. The randomization and stratification will minimize any influence in the variability of SoC.

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

The enrollment will be stratified based on criteria in Section 4.4:

Enrollment will be paused for evaluation of safety and efficacy after the enrollment of the first 40 patients and the first meeting of the DSMB will occur within the first week of enrolling the 40th patient. No further patients will be enrolled until the completion of this DSMB review and the safety and efficacy data from the first 40 patients will be shared with the FDA prior to resuming enrollment.

A dose of 20 mg selinexor or matching placebo will be administered orally on Days 1, 3, and 5 of each week for up to 2 weeks. If the patient is tolerating therapy and clinically benefitting (i.e., not meeting any of the criteria for stopping therapy listed below), dosing can continue for an additional 2 weeks (on Days 15, 17, 19, 22, 24, and 26). It is recommended that patients are dosed with study drug within 12 hours of providing consent.

Patients who achieve ANY of the following criteria will be considered as having clinical benefit for the purpose of continuing dosing for an additional 2 weeks.

1. Patient remains hospitalized and:
    a. Has not had a selinexor-related Grade 4 AE or selinexor-related serious AE (SAE)

       AND

    b. Has not had >1 point ordinal score reduction (worsening)

       OR

    c. Has 2 point reduction (worsening) in ordinal score with a ≥20% absolute reduction in FiO_2 from peak oxygen requirement
2. Patients discharged from the hospital before Day 28 must meet the following criteria in order to continue on selinexor:
    a. Platelet count >75,000/mm^3 and
    b. Neutrophil count >1,000/mm^3 and
    c. Serum sodium >130 mmol/L and
    d. No Grade ≥3 nausea or vomiting and

e. No Grade 4 AEs considered to be related to selinexor and

f. Improved ordinal score from baseline and

g. Positive SARS-CoV2 by FDA approved laboratory test at discharge

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 and selinexor has shown marked inhibition of viral replication in vitro with an IC_{90} of ~100 nM. Inhibition of XPO1 by the SINE selinexor could induce both anti-viral and anti-inflammatory activity.

3.3. Justification for Dose

3.4. End of Study Definition

End of Study will occur when the last patient has completed the 30-day Safety follow up period (after their last dose of study treatment), has withdrawn consent or has died, whichever comes first.

4. STUDY POPULATION

Eligible patients are adults ≥18 years of age, admitted to the hospital, confirmed laboratory diagnosis of SARS-CoV2 infection. All patients, their proxies must provide signed written or verbal informed consent. The Informed Consent Form (ICF) and the process to obtain the informed consent will comply with all local laws, regulations, and guidance.

4.1. Inclusion Criteria

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

1. Age ≥18 years
2. Confirmed laboratory diagnosis of SARS-CoV2 by standard FDA-approved RT-qPCR assay or equivalent FDA-approved testing (local labs) within 7 days of enrollment.
3. Currently hospitalized.
4. Informed consent.
5. Has symptoms of severe COVID-19 as demonstrated by:
   a. At least one of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion, or symptoms of severe lower respiratory symptoms including dyspnea at rest or respiratory distress.
   b. Clinical signs indicative of lower respiratory infection with COVID-19, with at least one of the following: SaO2 <92% on room air in last 12 hours or requires ≥4 LPM oxygen by nasal canula, non-rebreather/Ventimask (or similar device) or high flow nasal canula in order to maintain SaO2 ≥92%, PaO2/FiO2 <300 mm/hg. Patients with COPD or chronic lung disease must demonstrate evidence of increased oxygen needs above baseline.
6. Elevated CRP > 2 x ULN
7. Concurrent anti-viral and/or anti-inflammatory agents (e.g., biologics, hydroxychloroquine) are permitted. If in the physician's judgement, it is in the best interest of the patient to use anti-viral or anti-inflammatory treatments, these treatments are to be documented in the patient's chart and entered in the electronic case report form.

   Note: Patients who may have received plasma convalescent therapy > 48 hours prior to enrollment with no clinical improvement and who still meet criteria for severe COVID-19 may enroll. On study plasma convalescent therapy is not permitted.

   Patient who receive plasma convalescent therapy within 48 hours may be permitted to enroll based on discussion with sponsor.
8. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients must use highly effective methods of contraception throughout the study and for 3 months 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. Respiratory failure (defined by endotracheal intubation and mechanical ventilation, oxygen delivered by noninvasive positive pressure ventilation, or clinical diagnosis of respiratory failure in setting of resource limitations)
    b. Septic shock (defined byinvestigator assessment or requires vasopressor)
    c. Multiple organ dysfunction/failure
2. In the opinion of the investigator, unlikely to survive for at least 48 hours from screening
3. Inadequate hematologic parameters as indicated by the following labs:
    a. Patients with severe neutropenia (ANC <1000 x 10^9/L) or
    b. Thrombocytopenia (e.g., platelets <100,000 per microliter of blood)
4. Inadequate renal and liver function as indicated by the following labs:
    a. Creatinine clearance (CrCL) <20 mL/min using the formula of Cockcroft and Gault.
    b. Aspartate transaminase (AST) or alanine transaminase (ALT) > 5 x upper limit of normal (ULN)
5. Hyponatremia defined as sodium < 130 mEq/L
6. Unable to take oral medication when informed consent is obtained.
7. Patients with a legal guardian or who are incarcerated.
8. Treatment with strong CYP3A inhibitors or inducers. A list of strong CYP3A inhibitors and inducers is provided in Appendix 3.
9. Pregnant and breastfeeding women.

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/Stratification

Randomization will be performed prior to dosing.

Randomization will be stratified based on the following stratification factors and will maintain the 2:1 allocation between treatment arms (selinexor vs placebo) within each of the stratification categories:

- 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).

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

- High Risk Comorbidities: Age > 75, BMI> 30, cancer patients on chemotherapy, patients with cardiac (CAD, AMI, CHF) or pulmonary (COPD, emphysema) disease, diabetes, hypertension. Stratification will be based on number of high risk comorbidities: (1 vs ≥2 vs 0)

5. STUDY TREATMENT

5.1. 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

A dose of 20 mg selinexor or matching placebo will be administered orally on Days 1, 3, and 5 of each week for up to 2 weeks. If the patient is tolerating therapy and clinically benefitting (defined below), dosing can continue for an additional 2 weeks (on Days 15, 17, 19, 22, 24, and 26).

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.

Eligible patients must be able to take oral medication when informed consent is obtained. If a patient is later intubated or unable to take oral medication during treatment, it is permissible to use selinexor suspension prepared as below:

A suspension of selinexor and/or placebo can be prepared by the site pharmacy from selinexor tablets, water, and the commercial suspension agent Ora-Blend®. The pharmacy should place one 20 mg active or placebo tablet in a bottle (amber if available) and add 3 mL of water to disintegrate the tablet, then add 9 mL of Orablend® suspending agent. Gentle swirling or

inversion of the capped bottle will mix the suspension and suspend selinexor for dosing. The resulting suspension should be dosed within 4 hours. Administer the suspension to the patients using an oral dosing syringe via a nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) feeding tube. Rinse the bottle, syringe and tube with 40 mL to 110 mL of saline and dose the saline rinse to the patient to ensure complete delivery of the selinexor/placebo dose.

Handling Precaution: Selinexor tablets are coated for easy handling. Do not break, cut, or crush selinexor tablets because of increased risk of dermatologic toxicity (e.g., rash) from exposure to the active ingredient in the tablets.

Handling Precaution: The tablets quickly disintegrate in water (<10 min) without being crushed. Please wear gloves when handling the suspension to prevent unintended exposure to the active ingredient. The site pharmacy should consult the pharmacy manual for full instructions on preparing and handling the suspension and for alternative suspending agents should Ora-Blend® be unavailable.

5.3. Missed or Vomited Doses of Selinexor

5.3.1. Missed Doses of Selinexor

Missed selinexor doses should be managed as follows:

- If a dose was missed, the dose should be taken the next day. Subsequent doses must respect the required 48 hour interval planned schedule. All missed and delayed doses should be documented
- If a dose must be skipped (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. All missed and delayed doses should be documented.

5.3.2. Vomited Doses of Selinexor

If a dose is vomited ≤1 hour after ingestion and an intact tablet is seen, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

5.4. 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 (i.e., receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.5. 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.

5.6. Concomitant Medication

5.6.1. Recommended Concomitant Treatments

Provide prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-emetic agents prior to and during treatment with selinexor.

Ensure that patients are maintaining adequate fluid status and administer intravenous hydration as clinically warranted during the study treatment.

5.6.2. Prohibited/Permitted Concomitant Medications

If in the physician's judgement, it is in the best interest of the patient to use anti-viral or anti-inflammatory treatments, these treatments are to be documented in the patient's chart and entered in the electronic case report form. Use of these treatments should be carefully considered as they could potentially confound data interpretation.

The use of strong CYP3A inhibitors or inducers while on selinexor treatment is not permitted. Selinexor should be interrupted during the use of these agents. See Appendix 3 for a list of strong CYP3A inhibitors and inducers.

5.7. 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.

Selinexor should be discontinued for all selinexor-related life-threatening (Grade 4) AEs.

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
20 mg Days 1, 3 and 5 of each week (60 mg total per week)	20 mg Days 1 and 3 weekly (40 mg total per week)

Table 5: Selinexor Dosage Modification for Adverse Reactions

Adverse Reaction[a]	Occurrence	Action
Hematologic Adverse Reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 50,000/mcL	Any	• Reduce selinexor by 1 dose level (see Table 4).
Platelet count 25,000 to less than 50,000/mcL *with* concurrent G3 bleeding	Any	• Interrupt selinexor and provide appropriate supportive care. • Restart selinexor after bleeding has resolved at 1 dose level lower (see Table 4).
Platelet count less than 25,000/mcL	Any	• Interrupt selinexor and provide appropriate supportive care. • Monitor until platelet count returns to at least 50,000/mcL. • Restart selinexor at 1 dose level lower (see Table 4).
Neutropenia		
Absolute neutrophil count of 0.5 to 1.0 x 10^9/L *with* fever	Any	• Interrupt selinexor and provide provide appropriate supportive care. • Monitor until neutrophil counts return to 1.0 x 10^9/L or higher. • Restart selinexor at 1 dose level lower (see Table 4).
Absolute neutrophil count less than 0.5 x 10^9/L	Any	• Interrupt selinexor and provide appropriate supportive care. • Monitor until neutrophil counts return to 1.0 x 10^9/L or higher. • Restart selinexor at 1 dose level lower (see Table 4).
Anemia		
Hemoglobin less than 8.0 g/dL	Any	• Reduce selinexor by 1 dose level (see Table 4). • Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences	Any	• Interrupt selinexor and administer appropriate care with blood transfusions and/or other treatments per clinical guidelines. • Monitor until patient stabilizes and hemoglobin is >8.0 g/dL. • Restart selinexor at 1 dose level lower (see Table 4).
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.

Adverse Reaction[a]	Occurrence	Action
		• Restart selinexor at 1 dose level lower (see Table 4).
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 additional 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 1 dose level lower (see Table 4)
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 4). • 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 4).
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 dose level lower (see Table 4).
Other Adverse Reactions		
Grade 3 or 4 non-hematologic reactions	Any	• Interrupt selinexor. • Monitor until resolved to Grade 2 or lower, restart selinexor at 1 dose level lower (see Table 4).
Life-threatening hematological and non-hematological (Grade 4) AEs *related* to selinexor	Any	• Discontinue selinexor

[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.

Selinexor should be discontinued for all selinexor-related life-threatening (Grade 4) AEs.

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. Waivers for eligibility criteria for enrollment will not be permitted. The criteria given below are reasons the investigator must consider for removal of patients from study.

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 electronic case report form (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.
- Worsening clinical condition defined as at least 5 days of intubation/ECMO with no evidence of clinical improvement. Patients who are clinically stable based on oxygen requirements on mechanical ventilation will be permitted to remain on study.
- Grade ≥3 nausea or vomiting despite optimal antiemetic therapy.
- Progression of renal dysfunction requiring dialysis.
- Grade 4 AEs related to selinexor.

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. Blinding

The site investigators and patients are blinded to treatment assignment during the conduct of the study. All study staff will be blinded to the treatment assignments and study drug will be administered in a blinded manner.

Unblinding of treatment assignments should be undertaken for safety reasons when it is essential for effective treatment of the patient.

Unblinding is performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The Investigator will then receive details of the drug treatment for the specified patient.

The entire study population will be unblinded at the end of the study and the unblinding information will be shared with each study site.

6.5. 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 independent ethics committees (IECs), institutional review boards (IRBs), Investigators, and regulatory authorities.

6.6. End of Study

End of Study will occur when the last patient has completed the 30-day Safety follow up period (after their last dose of study treatment), has withdrawn consent or has died, whichever comes first.

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 (e.g., blood count) and obtained prior to signing of the informed consent form (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, ethnicity, and race) will be collected.

7.1.2. Medical History

The medical history will include co-infections, 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.

7.1.3. Disease History

The disease history will include collection of COVID-19 symptom onset date as well as date and time of admission to hospital and reason for admission (COVID-diagnosis/COVID associated complication or Concomitant Illness).

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
  - If patient requires respiratory assistance, then type of assistance, start and end date as well as reason for removal of mechanical ventilation will be documented in the eCRF.

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. Ordinal Score

The Ordinal score is a composite measure of clinical improvement and/or survival, assessed on a daily basis.

The severity rating is on a 8-point ordinal scale:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
7. Not hospitalized, limitation on activities and/or requiring home oxygen;
8. Not hospitalized, no limitations on activities.

7.3.3. 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.

7.3.4. 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
Coagulation		
PT	aPTT	INR

Blood samples 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 (e.g., 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.

7.3.5. 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).

7.3.5.1. 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) and at the end of treatment. Pregnancy testing may be performed if clinically indicated during the study.

7.4. Pharmacokinetic Assessments

Pharmacokinetic (PK) assessment will be performed on a subset of patients. Blood draws for PK analysis of approximately 2.0 mL will be collected for the measurement of plasma concentrations of selinexor at 4 ± 1 hr, 24 ± 4 hr post dose on Day 1 and predose on Days 3 and 5. Instructions for the collection and handling of biological samples are provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample and selinexor dose will be recorded.

If a patient experiences emesis within the first hour of selinexor dosing, no PK samples will be collected for that dose.

Plasma PK samples will be shipped to a bioanalytical laboratory for analysis. Details for collection and processing of PK samples can be found in the Laboratory Manual. Plasma samples will be analyzed via a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor.

7.5. Cytokine Assessments

Blood draws for cytokine analysis of approximately 2.5 mL will be collected according to the Schedule of Assessments Table. We will be testing cytokines and other plasma proteins and compare their levels to assess the efficacy of selinexor in the reduction of cytokines known to be elevated in COVID-19 patients. Exact details on the collection, preparation, storage and delivery of the samples will be included in the Clinical Protocol Lab manual.

7.6. Leukocyte Phenotyping

For Leukocyte Phenotyping, blood will be collected according to the Schedule of Assessments Table. Exact details on the collection, preparation, storage and delivery of the samples will be included in the Clinical Protocol Lab manual.

7.7. Viral Assessments

CCI

[redacted]

8. ADVERSE EVENTS

8.1. Information on Reporting 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.
- *Life-threatening adverse event or life-threatening suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- *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. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (See Section 8.2.1.3 for additional information about SAE reporting.)
- *Suspected adverse reaction*: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.
- *Unexpected adverse event or unexpected suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent

with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not but are not specifically mentioned as occurring with the particular drug under investigation.

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.

Investigators should use medical judgment in determining whether a particular symptom or sign is considered to be a part of COVID-19 infection clinical course or not and report them or not as AEs according to such determination. When a clear determination cannot be made by the investigators, a sign or symptom should be reported as AEs. All deaths irrespective of cause of death including due to COVID-19 during the study should be reported to the Sponsor using an SAE form.

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 (i.e., 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 (e.g., 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 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. 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 (e.g., '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 strong 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 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).

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 should be reported to the Karyopharm PV department using a SAE form.

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 with the timeframe not to exceed 24 hours of the Investigator becoming aware of the event. 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 (i.e., 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.

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. Sample Size Determination

Approximately 247 patients CCI [redacted]

9.3. Populations for Analyses

The intent-to-treat (ITT) population will consist of all patients who are randomized in the study with confirmed SARS-CoV2 infection under protocol version 6.0 and above, regardless of whether or not they receive study treatment.

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.

9.4. Statistical Analyses

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections.

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

9.4.1. Efficacy Analyses

Efficacy analyses will be performed in ITT population. If the primary endpoint, (Day 14 OSI), is significant, the 4 key secondary endpoints will be sequentially tested in the order listed below. If

any null hypothesis is not rejected in this sequence of tests, formal sequential testing will be stopped and the analyses of any endpoints thereafter will be nominal only.

- Time to recovery defined as improvement from baseline score of 3 to ≥4 or from a baseline score of 4 to ≥5
- Proportion of patients with at least a 2 point improvement (increase) in the Ordinal Scale from baseline to Day 7.
- Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 7
- Proportion of patients with at least a 1 point improvement (increase) in the Ordinal Scale from baseline to Day 14.
- Time to an improvement of 2 point using WHO Ordinal Scale Improvement (TTCI-2)
- Time to clinical improvement (TTCI-1): defined as the time from randomization to an improvement of 1 point on the Ordinal Scale
- Overall Death rate on Day 28 (DR)
- Rate of mechanical ventilation (RMV)

The difference in binary endpoints between treatment arms will be calculated with a 95% confidence interval (CI). Comparison of the these endpoints between the 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.

The analysis of time to event endpoints will be performed by treatment arm based on a log-rank test. The median 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.

Analyses of all other secondary endpoints will be nominal only. Details will be specified in the SAP.

9.4.2. 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.

9.4.3. Pharmacokinetic Analysis

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

9.4.4. Pharmacodynamic Analysis

Plasma proteins will be assessed and quantified by immunoassays and multiplex assays when possible in a central lab.

9.4.5. Viral Analysis

Viral testing will be assessed and quantified.

9.5. Criteria for Stopping the Study

The criteria to halt the study will depend on the number of patients enrolled at the time of the analysis as described below:

A. If the overall number of patients enrolled is ≤60 patients, the study will be halted if any 1 of the following conditions are met at an IA or Data Safety Monitoring Board (DSMB) meeting:
    1. The absolute difference in the death rate in the treatment arm versus the control arm is >30%
    2. The absolute difference in the need for invasive ventilation in the treatment arm versus the control arm is >30%
    3. The absolute difference in the rate of Grade 3 or 4 nausea or vomiting in the treatment arm versus the control arm is >20%
B. If the overall number of patients enrolled is >60 patients, the study will be halted if any 1 of the following conditions are met at an IA or DSMB meeting:
    1. The absolute difference in the death rate in the treatment arm versus the control arm is >20%
    2. The absolute difference in the need for invasive ventilation in the treatment arm versus the control arm is >20%
    3. The absolute difference in the rate of Grade 3 or 4 nausea or vomiting in the treatment arm versus the control arm is >20%
C. If the overall number of patients enrolled is >120 patients, the study will be halted if any 1 of the following conditions are met at an IA or DSMB meeting:
    1. The absolute difference in the death rate in the treatment arm versus the control arm is >10%
    2. The absolute difference in the need for invasive ventilation in the treatment arm versus the control arm is >10%

3. The absolute difference in the rate of Grade 3 or 4 nausea or vomiting in the treatment arm versus the control arm is >10%

In addition, each IA includes a futility analysis which will determine if there is no significant improvement in the ordinal score in the treatment arm compared with the control arm.

9.6. Interim Analyses

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

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

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

1. favorable (CP ≥80%)
2. promising (30% ≤ CP <80%)
3. unfavorable (CP<30%)

The original planned total sample size of approximately 247 patients will be increased to achieve the targeted power of 80%, up to a maximum of 371 patients when the conditional power is in the promising zone. If the CP is <30%, the trial may be stopped for futility (non-binding). Otherwise, if the CP is ≥80% the total sample size will remain at 247 patients, and the trial continues as planned.

If the trial is not stopped at IAs and sample size is not changed based on the second IA, enrollment will continue until approximately 247 patients are enrolled, the final analysis will happen when all enrolled patients have had the chance to have the Day 14 OSI assessed.

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, adjust the sample size, 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

The Informed Consent Form (ICF) and the process to obtain the informed consent will comply with all local laws, regulations, and guidance. 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 informed consent will be obtained consistent with 21 CFR 50.24.

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 and for 3 months after the last dose. 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 or proxy 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 and for 3 months after the last dose. 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 (e.g., 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. 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 (e.g., 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.

10.4.3. 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. Any missing data must be explained. An audit trail will be maintained by the eCRF system

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.

10.4.4. 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 electronic data capture (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

At the interim analyses, primary efficacy outcome and/or 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 9.5). The DSMB will meet at least three times during the course of the study. Enrollment will be paused for evaluation of safety and efficacy after the enrollment of the first 40 patients and the first meeting of the DSMB will occur within the first week of enrolling the 40th patient. No further patients will be enrolled until the completion of this DSMB review and the safety and efficacy data from the first 40 patients will be shared with the FDA prior to resuming enrollment. The remaining DSMB meetings are planned to evaluate the data from the IA. The DSMB may also meet at other times during the study as needed.

The independent DSMB will be composed of at least 3 members who are independent of Karyopharm and the study. The DSMB will meet to evaluate safety and efficacy, to ensure the appropriate benefit risk profile for patients enrolled in the study and to review any SAEs that occur during the study. The DSMB will be provided with all reports of AEs including SAEs regardless of Investigator causality assessments.

Details on how the DSMB will review safety and response data are provided in the DSMB Charter. The DSMB review will include, but not be limited to, evaluations of duration of therapy and all cause and AE-related dose reductions, interruptions, and discontinuations. 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.

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.

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APPENDIX 1. SELINEXOR AS A THERAPEUTIC STRATEGY FOR SEPSIS

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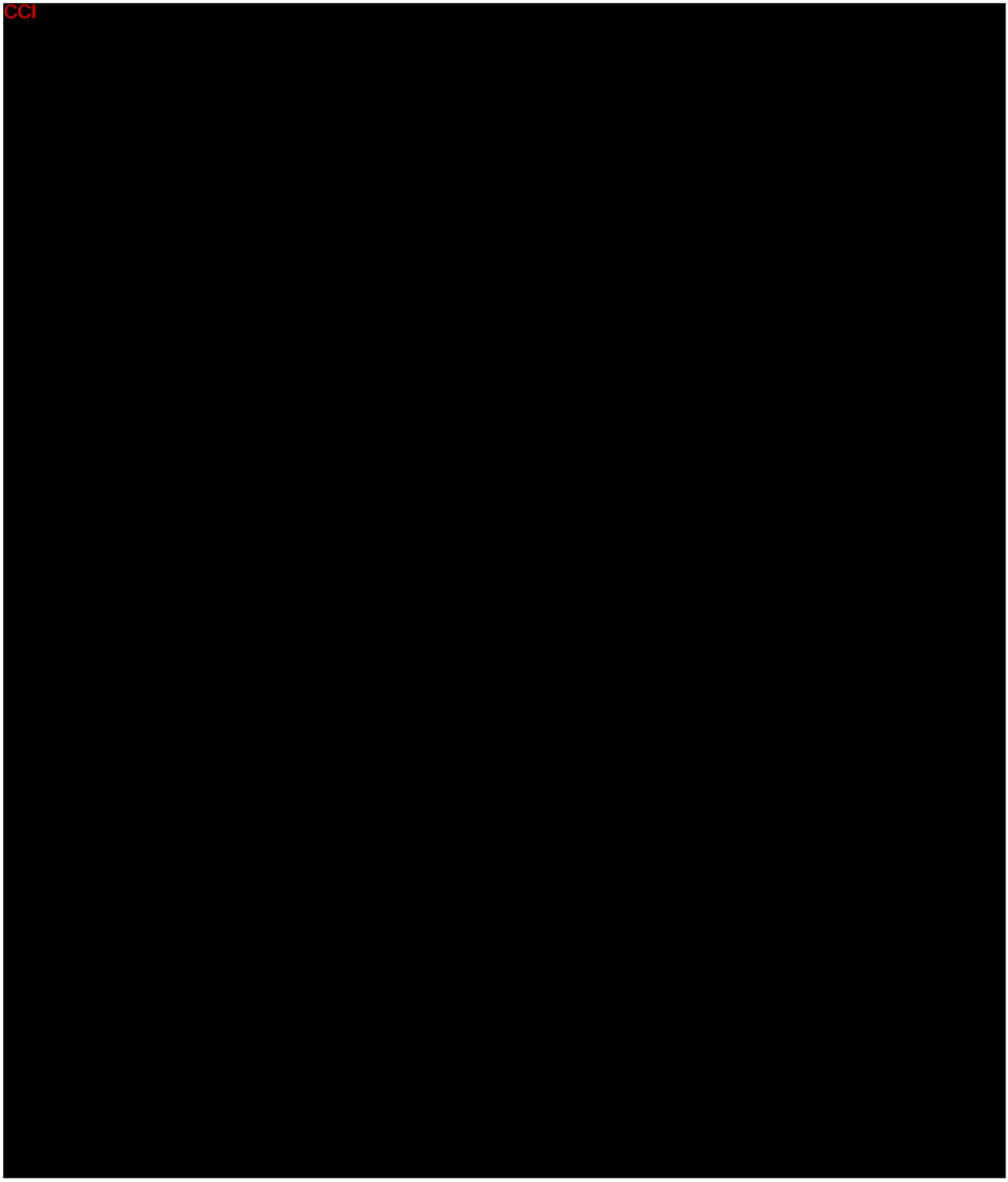

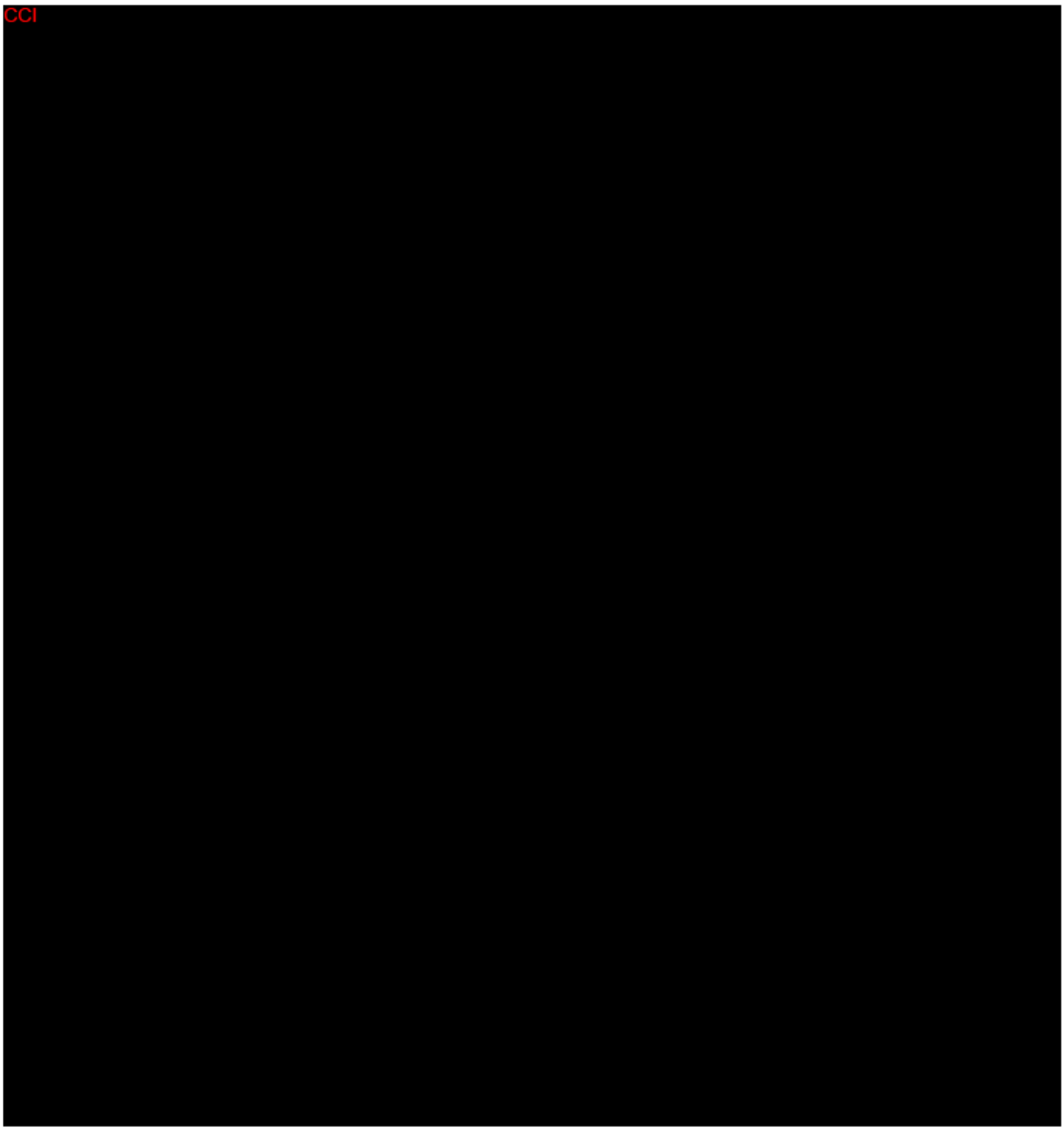
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APPENDIX 2. SAFETY AND TOLERABILITY OF SELINEXOR 20-MG DOSE

Please see the safety data available for the 20mg dose of selinexor (Table 7) These data were generated in two phase 1 studies evaluating escalating doses of selinexor in patients with heavily pretreated, progressive, relapsed refractory hematological malignancies and solid tumors.

- Study KCP-330-001: A Phase 1 Study of the Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced Hematological Malignancies; NCT01607892
- Study KCP- 330-002: A Phase 1 Study of the Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced or Metastatic Solid Tumor Malignancies; NCT01607905.

A summary of the findings from these studies are as follows: Twenty-five patients received a dose of ≤12 mg/m^2 (~20 mg) from two Phase 1 dose escalation studies in patients with advanced heavily pretreated hematologic (KCP- 330-001) and solid tumors (KCP- 330-002) and were included in the analysis. These patients had multiple lines of prior chemotherapy and were severely immunocompromised frail patients with heavily pre-treated relapsed refractory hematologic and solid tumors.
At a dose ≤12 mg/m^2 (≤ ~20 mg) in the first 2 weeks, the 5 most common non-hematologic adverse events (AEs) were low grade (Grade 1 and 2) nausea, decreased appetite, fatigue, vomiting and dysgeusia, that was manageable with supportive care. Hematologic AEs included only thrombocytopenia (Table 7) and the Grade 3 and 4 events (1 each) were observed in patients with refractory hematologic cancers (acute leukemia and myeloma). Note there were no grade 5 (death) events. There were no clinically significant changes in serum chemistries.
Nearly all of the adverse events were reversible and responded to supportive care. Finally, there were no clinically significant drug-drug interactions at these low doses, nor were any observed at much higher doses.
As these patients have refractory cancers that have progressed on available therapies, they will generally have more medical problems than the majority of the patients entering the proposed COVID-19 study, and therefore this represents a ‘worst case’ scenario.

***Conclusion*. Based on the data presented here, the highly selective and potent oral XPO1 inhibitors verdinexor and selinexor have no clinically important discernable differences, both have activity in models of sepsis, inflammation and influenza, and the adverse event profile of low dose selinexor consists of low grade, reversible and treatable symptoms.**

Table 7: Adverse Event (AE) Profile of Low Dose (≤20 mg) Selinexor from Phase 1 Studies in Patients with Advanced Refractory Hematologic and Solid Tumor Malignancies.

	Data From Phase 1 Studies in Patients with Heaviliy Pretreated Advanced Hematological and Solid Tumors (Studies KCP-330-001 and KCP-330-002) (N=25)									
	TEAEs with Onset <= Day 14 in ≥3 patients by Max Severity Grade									
	Any Grade		Grade 1		Grade 2		Grade 3		Grade 4	
AE Term	n	%	n	%	n	%	n	%	n	%
Nausea	19	76	11	44	8	32				
Decreased appetite	17	68	11	44	6	24				
Fatigue	15	60	3	12	12	48				
Vomiting	11	44	10	40	1	4				
Dysgeusia	9	36	8	32	1	4				
Headache	9	36	9	36						
Anaemia	7	28	2	8	3	12	2**	8		
Constipation	7	28	5	20	1	4	1	4		
Diarrhoea	6	24	6	24						
Hyponatraemia	6	24	5	20			1	4		
Weight decreased	6	24	6	24						
Abdominal pain	5	20	4	16	1	4				
Cough	4	16	3	12	1	4				
Dry mouth	4	16	4	16						
Thrombocytopenia	4	16	2	8			1#	4	1#	4
Dehydration	3	12	0	0	3	12				
Dizziness	3	12	2	8	1	4				
Dyspepsia	3	12	3	12						
Dyspnoea	3	12	2	8	1	4				
Flushing	3	12	3	12						
Hypotension	3	12	1	4	2	8				
Insomnia	3	12	2	8	1	4				
Photopsia	3	12	3	12						
Vision blurred	3	12	2	8	1	4				

* No grade 5 event occurred

**1 patient with Multiple Myeloma, 1 patient with Non-Hodgkin's Lymphoma

#Grade 3 event from a patient with Acute Myeloid Leukemia, Grade 4 event from a patient with Multiple Myeloma

APPENDIX 3. STRONG CYP3A INHIBITORS AND INDUCERS

Type	Example Medications
Strong CYP3A inducers	Apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampin, rifapentine, St John's Wort extract
Strong CYP3A inhibitors	VIEKIRA pak, indinavior/RIT, tipranavir/RIT, ritonavir, cobicistat (GS-9350), ketoconazole, indinavir, troleandomycin, telaprevir, danoprevir / RIT, elvitegravir / RIT, saquinavir / RIT, lopinavir / RIT, itraconazole, voriconazole, mifepristone, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice DS, ceritinib, conivaptan, nefazodone, nelfinavir, aquinavir, ribociclib, idelalisib , boceprevir

Note: This is based on Metabolism and Transport Drug Interaction Database (https://www.druginteractioninfo.org/), and is not an exhaustive list. For an updated FDA list, see the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#cypEnzymes.