A RANDOMIZED OPEN LABEL PHASE 2B/3 STUDY OF THE SAFETY AND EFFICACY OF NP-120 (IFENPRODIL) FOR THE TREATMENT OF HOSPITALIZED PATIENTS WITH CONFIRMED COVID-19 DISEASE

INVESTIGTIONAL PRODUCT:	Ifenprodil tartrate (NP-120)
IND/CTA NUMBER:	148484/238605
EUDRACT NUMBER:	2020-002746-16
PROTOCOL NUMBER:	AGN120-3
PHASE:	2b/3
PROTOCOL VERSION AND DATE:	Version 2.0 2020-11-16
SPONSOR ADDRESS	Algernon Pharmaceuticals 915 – 700 West Pender Street Vancouver, BC, Canada V6C 1G8

CONFIDENTIAL

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CLINICAL STUDY PROTOCOL

Title: A Randomized Open Label Phase 2b/3 Study of the Safety and Efficacy of NP-120 (Ifenprodil) for the Treatment of Hospitalized Patients with Confirmed COVID-19 Disease

Protocol Number:	AGN120-3
IND/CTA Number:	148484/238605
EudraCT Number:	2020-002746-16
Investigational Product:	Ifenprodil tartrate (NP-120)
Version and Date:	v. 2.0 (2020-11-16)
Product Sponsor:	Algernon Pharmaceuticals 915 – 700 West Pender Street Vancouver, BC, Canada V6C 1G8
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PROTOCOL APPROVAL

Protocol Title:	A Randomized Open Label Phase 2b/3 Study of the Safety and Efficacy of NP-120 (Ifenprodil) for the Treatment of Hospitalized Patients with Confirmed COVID-19 Disease
Protocol Number:	AGN120-3
Protocol Date:	2020-11-16

Nov 18/2020
Date

Mark Williams Ph.D.
Chief Scientific Officer
Algernon Pharmaceuticals

INVESTIGATOR AGREEMENT

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Algernon Pharmaceuticals or their designee and the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB or IEC responsible for this study.

I further agree that Algernon Pharmaceuticals or their designee shall have access to any source documents from which CRF information may have been generated.

_____
Printed Name of Investigator

_____
Title of Investigator

_____
Signature of Principal Investigator Date

PROCEDURES IN CASE OF EMERGENCY

Table 1 Emergency Contact Information

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1. PROTOCOL SYNOPSIS

TITLE: A Randomized Open Label Phase 2b/3 Study of the Safety and Efficacy of NP-120 (Ifenprodil) for the Treatment of Hospitalized Patients with Confirmed COVID-19 Disease

TRIAL DESIGN: Open-label, multi-center, randomized, parallel group study

This protocol is largely based on the recommendations of the WHO R&D Blueprint Clinical Trials Expert Group COVID-19 Therapeutic Trial Synopsis, and associated Master Protocol.

NUMBER OF STUDY CENTERS: Approximately 10

STUDY LOCATION: Canada, US, Australia, Philippines, Romania

PHASE OF DEVELOPMENT: 2b/3

INDICATION: Treatment of SARS-CoV-2 Infected Patients

INVESTIGATIONAL PRODUCT: NP-120 (Ifenprodil tartrate)

STUDY RATIONALE: NP-120 (Ifenprodil) is an N-methyl-D-Aspartate (NDMA) inhibitor that is specific for the NR2B subunit of the NMDA Receptor. The NMDA receptor, and specifically the NR2B subunit, is involved in glutamate signaling, and is expressed on both neutrophils and T cells. In the case of neutrophils, activation of the NMDA receptor can (1) result in expression of CD11b which targets neutrophils via ICAM-1 to areas of inflammation, and (2) trigger the autocrine release of glutamate. In the case of T-cells, activation of T cells via glutamate can cause (1) T cell proliferation and, (2) the release of cytokines. The activation of T cells and cytokine release can be blocked *in vitro* by the addition of Ifenprodil. As such it could be a potent anti-inflammatory agent.

Ifenprodil was discovered by a genome wide RNAi assay to uncover gene targets associated with cytoprotective activity against highly pathogenic H5N1 influenza, specifically by preserving cell viability in vitro. When tested in a murine model of H5N1, the drug at clinically relevant doses: (1) improved survivability from 0% at day 6 to 40% day 14 post-infection, (2) the drug significantly reduced edema and lung injury score and (3) reduced infiltrating T cells, neutrophils and NK cells and attenuated the 'cytokine storm'. The mortality rate of H5N1 in humans is >50%, whereas the mortality rate of SARS-CoV-2 infected patients is < 5%, and both viruses cause acute lung injury and share similar pulmonary pathologies. NP-120 has also been shown to mediate anti-inflammatory responses and reduce pulmonary fibrosis in a murine model of idiopathic pulmonary fibrosis, a complication which can occur after a respiratory virus infection.

Based on the fact that H5N1 has a significantly higher mortality rate than SARS-CoV-2 but still shares similar lung pathologies, Algernon Pharmaceuticals believes Ifenprodil could reduce lung injury associated with COVID-19 disease, thereby improving lung function and accelerating patient recovery.

The purpose of this Phase 2b/3 trial is to determine the safety and efficacy of NP-120 in the treatment of COVID-19 disease.

PRIMARY OBJECTIVES: To investigate the clinical efficacy and safety of NP-120 (20 and 40 mg TID) compared to standard of care in patients hospitalized with COVID-19 disease.

- The choice of the primary outcome measure for Phase 3 will be determined by a pilot Phase 2b study of the first 150 subjects.

- Subject clinical status (on the WHO7-point ordinal scale) at day 15 is the default primary endpoint

SECONDARY OBJECTIVES: To investigate the clinical efficacy of NP-120 (20 and 40 mg TID) as compared to the control arm as assessed by:

- **Ordinal scale:**
  - Time to an improvement of one category from baseline on an ordinal scale.
  - Subject clinical status on an ordinal scale at days 3, 5, 8, 11, and 29.
  - Mean change in the ranking on an ordinal scale from baseline to days 3, 5, 8, 11, 15 and 29 from baseline
- **National Early Warning Score (NEWS):**
  - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
  - Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS
- **Oxygenation:**
  - Oxygenation free days in the first 28 days (to day 29)
  - Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients
- **Mechanical Ventilation:**
  - Ventilator free days in the first 28 days (to day 29)
  - Incidence and duration of new mechanical ventilation use during the trial
- **Hospitalization:**
  - Duration of hospitalization (days)
  - Time to discharge (days)
- **Mortality:**
  - 15-day mortality
  - 28-day mortality

EXPLORATORY OBJECTIVES: To investigate the effects of NP-120 (20 and 40 mg TID) on lung function, health status, and SARS-CoV-2 RNA status in hospitalized patients with COVID-19 disease.

SAFETY OBJECTIVES: To study the safety of NP-120 (20 and 40 mg TID) in hospitalized patients with COVID-19 disease.

PATIENT POPULATION: Individuals with COVID-19 disease that are currently hospitalized, and either requiring supplemental oxygen, or non-invasive ventilation or high flow oxygen devices. This corresponds to a score of 4 or 5 (moderate and severe disease) on the WHO proposed ordinal scale for clinical improvement.

STUDY CONDUCT: The trial will be conducted in two stages:

1. A Pilot Stage (Phase 2b) and,
2. A Pivotal stage (Phase 3)

NUMBER OF SUBJECTS FOR THE PILOT STAGE OF THE STUDY: Approximately 150:

Treatment Arm A:	Ifenprodil (20 mg TID) on top of Standard of Care (N=50)
Treatment Arm B:	Ifenprodil (40 mg TID) on top of Standard of Care (N=50)
Control Arm:	Standard of Care (N=50)

For the pilot phase, a sample of approximately 150 patients (50 in Arm A, Arm B and SOC) will be recruited. To account for drop out of 10%, a total of 168 patients will be enrolled.

NUMBER OF SUBJECTS FOR THE PIVOTAL PHASE 3 STAGE OF THE STUDY:

For the pivotal phase, a sample of 462 patients (231 in the SOC group and 231 in the active treatment group/s) achieves 90% power to detect a change in the log odds ratio of 0.5596 when the significance level (alpha) is 0.05 using a two-sided test. A log odds ratio of 0.5596 corresponds to an odds ratio of 1.75 comparing treatment to SOC. To account for drop out of 10%, a total of 514 patients will be enrolled.

Phase 2b Interim analysis and increasing the patient number: An interim analysis will be conducted on the ITT population when 75 patients complete the clinical status assessment at day 15 (the primary endpoint). A preliminary full analysis report of 150 patients with up to Day 29 entered will also be presented. An interim analysis that allows stopping for futility or efficacy will be considered for Phase 3. Details for the Phase 3 futility or efficacy analysis will be specified in the Phase 3 Statistical Analysis Plan and DSMB Charter as appropriate.

PRIMARY EFFICACY PARAMETER: Patient clinical status (on the WHO 7-point ordinal scale) at day 15 in IP versus SOC control group patients:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
6. Hospitalized, on invasive mechanical ventilation or ECMO
7. Death

SECONDARY EFFICACY PARAMETERS:

- Status on an ordinal scale assessed daily while hospitalized and on days 15 and 28 in IP versus control group patients
- NEWS assessed days 3, 5, 8 ,11 while hospitalized and on days 15 and 29 in IP versus control group patients
- Rate of mechanical ventilation in IP versus control group patients
- Duration of mechanical ventilation (if applicable) in IP versus control group patients
- Duration of supplemental oxygen in IP versus control group patients
- Time to return to SpO2 > 94% on room air
- Duration in ICU (if applicable) in IP versus control group patients
- Rate of Mortality in IP versus control group patients
- Duration of hospitalization in IP versus control group patients
- Time to discharge in IP versus control group patients

- Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients

EXPLORATORY EFFICACY PARAMETERS:

- Changes in the extent of dyspnea from baseline, using a Likert scale, at Days 2, 4, 8, and 14 in IP versus control group
  [Likert scale: The patient grades his/her current breathing compared to when he/she first started the study (from -3 to 3). "0" = no change, "1" =minimally better, "2" =moderately better, "3" =markedly better, "-1" =minimally worse, "-2" =moderately worse, "-3" =markedly worse]. For the first questionnaire (at baseline), the patient compares their current shortness of breath to their shortness of breath when they are well.
- Rate of change to patient's experience of cough (Visual analog scale [VAS]) at Days 2, 4, 8, and 14 in IP versus control group
  VAS: The patient draws a vertical line on an axial graph (from 0 to 100) to show the degree of how he/she feels about coughing. The number "100" equals the worst coughing the patient has ever felt and the number "0" equals the best he/she has felt since baseline.
- Changes in D-dimer in IP versus control group
- Qualitative PCR for SARS-CoV-2 at baseline, days 5 (while hospitalized, and days 15 and 29 (if able to return to clinic or still hospitalized)
- Quantitative PCR (if available) for SARS-CoV-2 at baseline, days 5 (while hospitalized, and days 15 and 29 (if able to return to clinic or still hospitalized)

SAFETY PARAMETERS:

- Type, frequency, severity, and relationship of AEs to investigational product (IP)
- Number of patients who discontinue IP due to any AE
- Frequency of clinically significant changes in vital signs and/or laboratory findings

TREATMENT: Test Product: NP-120, 20 or 40 mg TID for up to 2 weeks (either to hospital discharge, or Day 14, whichever comes first). Patients who find it difficult to swallow pills can be administered crushed pills of NP-120 and fed via a naso-gastric tube.

Duration of subject participation*:* Up to 60 days (from screening to follow up on day 60 ± 3 days)

INCLUSION CRITERIA:

1. Male and female subjects aged ≥18 years of age
2. Confirmed coronavirus infection
   a) Positive real-time fluorescence polymerase chain reaction of the patient's respiratory or blood specimens for SARS-CoV-2 nucleic acid
   b) Viral gene sequences in respiratory or blood specimens that are highly homologous to SARS-CoV-2
   c) Any other diagnostic test accepted by local regulatory authorities
3. Must be hospitalized and requiring supplemental oxygen, or on non-invasive ventilation or high flow oxygen devices (Score of 4 or 5 on WHO Ordinal Clinical Scale)
4. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (e.g. oral contraceptives,

intrauterine device, diaphragm plus spermicide) from the time of screening and must agree to continue using such precautions for 90 days after the final dose of study drug(s)

5. Non-sterilized males who are sexually active with a female partner of childbearing potential must use condom plus spermicide from day 1 through 90 days after receipt of the last dose of study drug(s)
6. Subjects (or legal designate) must have the capacity to understand, sign and date a written, informed consent form and any required authorization prior to initiation of any study procedures

EXCLUSION CRITERIA:

1. Patients with vasodilatory shock, orthostatic hypotension, hypotension, or tachycardia at screening/baseline
2. Patients experiencing cerebral hemorrhage or cerebral infarction at baseline
3. ALT/AST > 5 times the upper limit of normal; Child-Pugh Score 10 to 15.
4. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
5. Patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
6. Patients taking droxidopa
7. Pregnant and lactating women and those planning to get pregnant
8. Known or suspected allergy to the trial drug or the relevant drugs given in the trial
9. Presence of other disease that may interfere with testing procedures or in the judgement of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial
10. Know inability of patient to comply with the protocol for the duration of the study
11. Involvement in a clinical research study within 4 weeks prior to screening and/or prior enrollment in the study or plan to participate in another interventional clinical trial during the study period. Participation in observational registry studies is permitted.

Schedule of Events:

Visit	Procedures
Visit 1 (Screening/Baseline/ Randomization, Days -1 to 1)	Informed Consent Inclusion/Exclusion Criteria SARS-CoV-2 RNA status testing Pregnancy test Demographics/medical history Vital signs (including SpO2) Physical Exam Clinical support data collection Safety laboratory testing Child-Pugh Score Cytokine MarkersPaO2 and PaO2/FiO2 ratio ECG VAS Extent of Dyspnea (Likert Scale) Concomitant medications Randomization Administer IP
Daily until hospital discharge or Visit 2 (Day 15)	Vital signs (including SpO2) Clinical support data collection

	SARS-CoV-2 RNA status testing (Day 5 or discharge, whichever comes first) Safety laboratory testing (Days 3, 5, 8, 11 if hospitalized) Child-Pugh Score (Days 3, 5, 8, 11 if hospitalized) Cytokine Markers PaO2 and PaO2/FiO2 ratio VAS (Days 2, 4, 8, and 14 if hospitalized) Extent of Dyspnea (Likert Scale, Days 2, 4, 8, and 14 if hospitalized) AEs recorded Concomitant medications IP administration (daily to discharge or Day 14)
Visit 2 – Day 15 (± 2 days)	Vital signs (including SpO2) Clinical support data collection SARS-CoV-2 RNA status testing Cytokine Markers Safety laboratory testing PaO2 and PaO2/FiO2 ratio VAS Extent of Dyspnea (Likert Scale) AEs recorded Concomitant medications
Visit 3 – Day 29 (± 2 days) Safety Follow Up Visit	Vital signs (including SpO2) Clinical support data collection SARS-CoV-2 RNA status testing (if viral RNA still detected on Day 15) Safety laboratory testing PaO2 and PaO2/FiO2 ratio VAS Extent of Dyspnea (Likert Scale) AEs recorded Concomitant medications
Visit 4 – Day 60 (± 3 days)	Vital Status AEs recorded

STATISTICAL CONSIDERATIONS:

Primary Efficacy Analysis: The SOC and treatment arms under WHO7 ordinal scale will be compared with respect to the primary endpoint using proportional odds models (ordinal logistic regression) adjusted for site and age. Treatment will be compared to SOC by testing whether the common odds ratio differs from 1.0 at day 15 using two-sided test at 2.5% level of significance under the ITT population set, followed by PP population set. All modeling assumptions will be verified.

Separate 95% CI and p-values will be computed across each of the ordinal scale between SOC and treatment arms for both ITT and PP population sets. Multiple comparison techniques (to be detailed in the SAP) will be employed to ensure type I error is controlled to 5% for these comparisons.

If, following the second interim analysis, the primary endpoint changes, details will be written in the SAP, and a protocol amendment will be created.

Sample size determination:

For the pilot Phase 2b phase, a sample of 150 patients (50 in Arm A, Arm B and SOC) will be recruited. To account for drop out of 10%, a total of 168 patients will be enrolled.

For the pivotal Phase 3 phase, A sample of 462 patients (231 in the SOC group and 231 in the active treatment group) achieves 90% power to detect a change in the log odds ratio of 0.5596 when the significance level (alpha) is 0.05 using a two-sided test. A log odds ratio of 0.5596 corresponds to an odds ratio of 1.75 comparing treatment to SOC. The sample size was estimated using the *Tests for Two Ordered Categorical Variables* module in PASS 14. To account for drop out of 10%, a total of 514 patients will be enrolled.
The sample size assumes that the distribution of patients on day 15 will be as shown in Table 2, which is scenario 4 in the WHO master protocol (2020) for enrolled patients with moderate to severe disease under an odds ratio of 1.75.

Table 2 Distribution of Patients Across Outcome Categories at Day 15: SOC (WHO MP Scenario 4) and Treatment (Assuming OR of 1.75)

	Percent of Patients	
Outcome	**SOC**	**Treatment**
7. Death	2	1.0
6. Hospitalized & on mechanical ventilation or ECMO	1	0.6
5. Hospitalized & on non-invasive ventilation or high flow O2	2	1.2
4. Hospitalized & requires supplemental O2	5	3.03
3. Hospitalized not requiring supplemental O2	17	11.45
2. Not hospitalized but limitations on activities	36	31.90
1. Not hospitalized & no limitations on activities	37	50.70

PREMATURE WITHDRAWAL/DISCONTIUNATION CRITERIA:

1. Patients who suffer vasodilative shock. However, physicians can use rescue therapy such as vasopressin to restore blood pressure and allow patients to continue in the study, at the discretion of the attending physician.
2. Patients whose ALT/AST rise to >5x upper limit of normal or Child-Pugh of 10-15.
3. Patients who experience a cerebral hemorrhage or cerebral infarction

TRIAL STOPPING RULES: The Medical Monitor team will review AE / SAE data every 2 weeks. If there are a concerning number of unexpected AEs, the DSMB will be asked to review safety data in an ad hoc meeting.

The DSMB will review safety data after every 25 subjects are entered into the trial up to 100 subjects, and then at every 50 subjects ad hoc reviews will be undertaken if there are other specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews. Based on the recommendations of the WHO R&D Blueprint Clinical Trials Expert Group and given the severity of illness in COVID-19, there are no pre-specified study stopping rules for safety.

For Phase 2b, an interim analysis will also be performed when 75 patients completed Day 15 assessments for the primary endpoint. For this interim analysis with first 75 patients with Day 15 efficacy data, in addition to standard DSMB outputs, the following descriptive statistics efficacy analysis will also be presented:

1. WHO-7 efficacy with Day 15 assessment
2. Status on an ordinal scale assessed daily while hospitalized and on days 15
3. NEWS assessed days 3, 5, 8 ,11 while hospitalized and on days 15 in IP versus control group patients
4. Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients
5. Rate of mechanical ventilation in IP versus control group patients (Patients who received Invasive/non-invasive Mechanical Ventilation by Day 15)

For item 5, if a patient did not experience mechanical ventilation by Day 15, he/she will be marked as a negative response even if the patient did experience mechanical ventilation past Day 15. This is different to the final analysis described above.

ANTICIPATED NUMBER OF PATIENTS PER SITE: TBD

ANTICIPATE START DATE/COMPLETION DATE: Q3 2020/Q1 2022

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LIST OF ABBREVIATIONS

°C	degrees Celsius
AE	adverse event
AM	before noon
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
BP	blood pressure
BUN	blood urea nitrogen
CFR	code of federal regulations
cm	centimetres
CRO	contract research organization
d	day
DSMB	data and safety monitoring board
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
e-CRF	electronic case report form
g	gram(s)
GCP	good clinical practice
GGT	gamma-glutamyltransferase
GMP	good manufacturing practice
HED	human equivalent dose
ICF	informed consent form
ICH	international conference on harmonization
ICMJE	international committee of medical journal editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
L	liter
LOCF	last-observation-carried-forward
MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
mmHg	millimetres mercury
MMRM	mixed model repeated measures
NEWS	National Early Warning Score
ng	nanogram
NOAEL	no-observed-adverse-effect level
pdf	portable document format
PM	after noon
PO	by mouth
PP	per-protocol
PTT	partial thromboplastin time
RBC	red blood cell(s)
SAE	serious adverse event

SAP	statistical analysis plan
SOC	standard of care
SOP	standard operating procedure
SRM	study reference manual
SUSAR	suspected, unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TID	three times per day
ULN	upper limit of normal
WBC	white blood cell(s)
wk	week(s)

2. INTRODUCTION

2.1 Background

COVID-19 is a severe respiratory infection caused by the SARS-CoV-2 virus. The disease occurs was first detected in China's Wuhan province in 2019 and spread globally over several months, in spite of efforts to quarantine infected patients. The disease is characterized by fever, dry cough, and fatigue. A minority of patients have symptoms such as nasal congestion, nasal discharge, sore throat, muscle pain, and diarrhea. Severe patients often suffer from dyspnea and/or hypoxemia one week after symptom onset, and severe patients can rapidly progress to acute respiratory distress syndrome, septic shock, difficult to correct metabolic acidosis, coagulation dysfunction and multiple organ failure. Most patients have a good prognosis and a minority are in critical condition; however, the prognosis of the elderly and those with chronic underlying diseases is more poor (Novel Coronavirus Pneumonia Diagnosis and Treatment Plan).

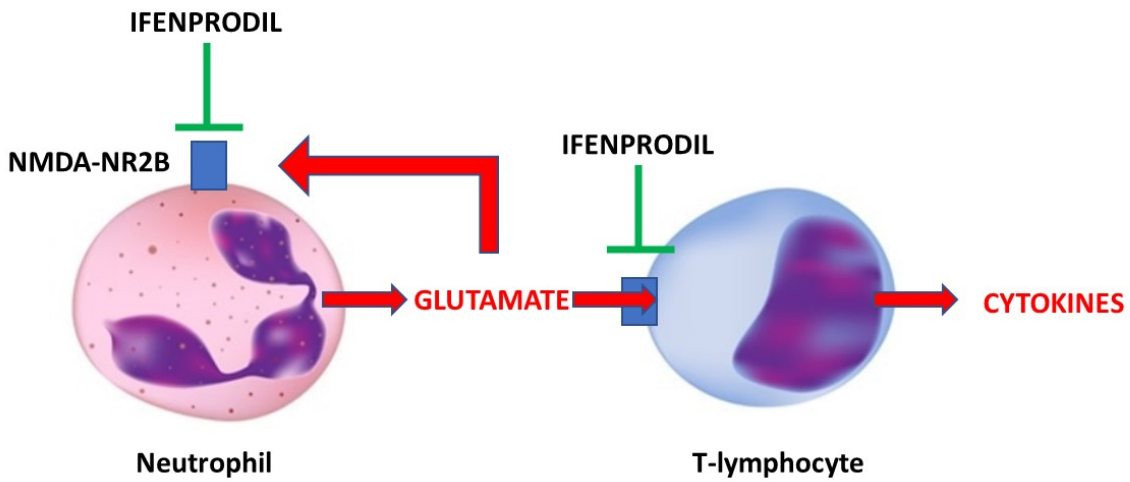
The mortality rate of the disease has yet to be determined but is generally estimated at <5%. An early published study showed that fatalities are often attributed to respiratory failure, and there is evidence that suggests that COVID-19 mortality might be due to a virus-activated "cytokine storm syndrome" (Ruan et. al., 2020).

2.2 Study rationale

Ifenprodil, an NMDA antagonist, specifically targeting the NR2B subunit, with a piperidinoalkanol structure, was first approved in Japan in 1971. It was developed as a vasodilator and has been used in Japan in the treatment of dizziness and vertigo, as well as in France in the treatment of Peripheral Arterial Obstructive Disease (Williams, 2001). Due to the widespread use of Ifenprodil in Japan and France, the safety, tolerability and pharmacokinetics of the drug are well established. The drug was also approved in South Korea in 2003.

The N-methyl-D-aspartate receptor (NMDAr) is historically regarded as a neurological target, but its functional expression has been reported in pulmonary tissue. The NMDAr is activated by glutamate (Glu), the main excitatory neurotransmitter which acts on receptors in the central nervous system (CNS). But overactivation of these receptors can cause several damages to neural cells including death. However, the target is also important for immunological function. The NMDA receptor, and specifically the NR2B subunit is expressed on both neutrophils (Del Arroyo, 2019) and T cells (Kahlifuss, 2014). In the case of neutrophils, activation of the NMDA receptor can (1) result in expression of CD11b which targets neutrophils via ICAM-1 to areas of inflammation (Li, 2015), and (2) trigger the *autocrine* release of glutamate. In the case of T-cells, activation of T cells via glutamate can cause (1) T cell proliferation and, (2) the release of cytokines. The activation of T cells and cytokine release can be blocked *in vitro* by the addition of Ifenprodil. Recent studies have also shown that the glutamate agonist N-methyl-D-aspartate can trigger acute lung injury (ALI).

Figure 1 Putative Mechanism of Ifenprodil on Glutamate Signaling in Neutrophils and T cells



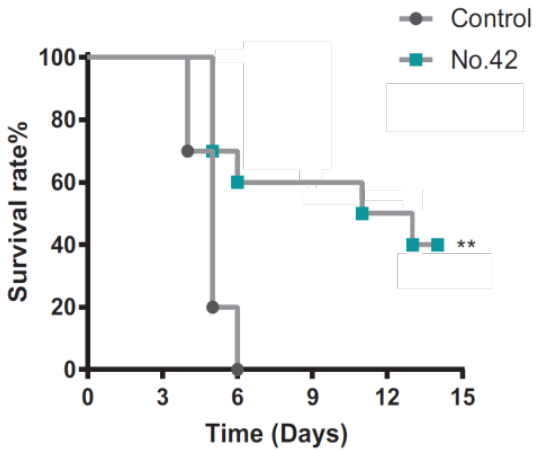
ALI is a direct and indirect injury to alveolar epithelial cells and capillary endothelial cell, causing diffuse pulmonary interstitial and alveolar edema and acute hypoxic respiration failure (Zhe et. al., 2018). ALI is characterized by reduced lung volume and compliance, and imbalance of the ventilation/perfusion ratio, inducing hypoxemia and respiratory distress and its severe stage (oxygen index <200) known as acute respiratory distress syndrome (ARDS). ARDS is a common, devastating clinical syndrome of acute lung injury with high mortality ranging from 40% to 60%. Furthermore, pathological findings show that 64% of ARDS patients may have pulmonary fibrosis (PF) during convalescence (Qiao et. al., 2009).

Antagonism of glutamate signaling could therefore ameliorate some of the complications of ALI and thereby also prevent the development of PF.

A recent paper from an independent group in China, found that repurposing ifenprodil could be useful for preventing virus-induced acute lung injury (Zhang et. al., 2019). A genome wide RNA interference (RNAi) screen was performed to identify gene targets that could rescue lung cell viability from H5N1 infection *in vitro*. Drug bank searches for compounds that could affect the same gene targets as were identified by the RNAi screen selected ifenprodil as a lead for further testing in an *in vivo* mouse model of H5N1 infection. The H5N1 is a highly lethal infection in humans with a >50% mortality rate, far larger than the estimated overall mortality rate of COVID-19 disease at <5%.

Notably, treatment with ifenprodil was able to significantly increase the survival of H5N1-infected mice: after 6 days, survival was 60% in the treatment group vs. 0% in the control group, and after 14 days, survival was 40% of ifenprodil-treated animals (see figure inline; No.42 refers to ifenprodil). In addition, several markers of lung function improved significantly including the lung injury score, the lung wet/dry ratio and the infiltrating cell count, in particular T cells and neutrophils. Multiple proinflammatory cytokines/chemokines which are elevated in the “cytokine storm” associated with viral infection were also significantly reduced.

Figure 2 Survival Rates of H5N1 Infected Mice after Treatment with Ifenprodil



(Zhang et al., 2019).

Early clinical reports suggest that the COVID-19 mortality might be due to virus activated "cytokine storm syndrome" or fulminant myocarditis, the latter of which could be addressed by Ifenprodil treatment (Ruan et al., 2020).

The ability of Ifenprodil to reduce pulmonary fibrosis was demonstrated using a murine bleomycin-induced IPF model (see Investigator's Brochure for details). In this experiment, disease severity as measured histologically was significantly reduced in animals treated with Ifenprodil versus control animals who received vehicle treatment. Ifenprodil was also tested in a guinea pig citric acid tussive model using Gefapixant as a positive control. Ifenprodil was found to significantly reduce both coughing frequency and onset of first cough. Pulmonary fibrosis also correlates with outcome in adult respiratory distress syndrome (Martin et. al., 1995).

The purpose of this trial is to determine the clinical efficacy of Ifenprodil in the treatment of patients with COVID-19 disease. This Protocol is largely based on the recommendations of the WHO R&D Blueprint Clinical Trials Expert Group COVID-19 Therapeutic Trial Synopsis, and associated Master Protocol.

The choice of the primary outcome measure for Phase 3 will be determined by a pilot Phase 2b study of the first 150 subjects. Subject clinical status (on a 7-point ordinal scale) at day 15 in treatment versus the control group is the default primary endpoint.

2.3 Risk/Benefit analysis

Currently, neither a vaccination nor a cure is available for COVID-19 disease. Treatment is performed on the basis of symptom management, prevention and management of complications, treatment of underlying diseases, prevention of secondary infections, and prompt support of organ functions. Respiratory support (including oxygen therapy, mechanical ventilation, and extracorporeal membrane oxygenation) is indicated in severe cases. The use of antiviral therapy (interferon-α, lopinavir/ritonavir, ribavirin, chloroquine phosphate, and umifenovir) has been proposed, but data on the effectiveness of these agents are not yet available. Use of tocilizumab has been suggested for patients with extensive and bilateral lung disease and severely ill patients with elevated IL-6 levels; however, this agent is contraindicated in patients with active infections. For patients with progressively deteriorating oxygenation index, rapid

imaging progression, and overactive inflammatory responses, short-term (3-5 days) glucocorticoid treatment may be used; however, the immunosuppressive function of high-dose glucocorticoid may delay the clearance of coronavirus from the system. There remains an unmet need for a therapy which can reduce levels proinflammatory cytokines and ameliorate lung injury without inhibiting the immune system.

Ifenprodil has a well-established safety record, having been used in Japan and France for almost 50 years. In addition, a review of 8 years of post-marketing surveillance in over 15,000 patients revealed no serious side effects.

Overall, based on the medical need and on the available Ifenprodil safety, tolerability, and efficacy data, the proposed Phase 2b/3 clinical trial design is considered appropriate and potential benefits of evaluating Ifenprodil in the study outweigh the perceived risks.

3. OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary objective:

- To investigate the clinical efficacy and safety of NP-120 (20 and 40 mg TID) compared to standard of care in patients hospitalized with COVID-19 disease.
    - The choice of the primary outcome measure for Phase 3 will be determined by a pilot Phase 2b study of the first 150 subjects.
    - Subject clinical status (on the WHO 7-point ordinal scale) at day 15 is the default primary endpoint

Secondary objectives:

- To investigate the clinical efficacy of NP-120 (20 and 40 mg TID) as compared to the control arm as assessed by:
    - Ordinal scale:
        - Time to an improvement of one category from baseline on an ordinal scale.
        - Subject clinical status on an ordinal scale at days 3, 5, 8, 11, and 29.
        - Mean change in the ranking on an ordinal scale from baseline to days 3, 5, 8, 11, 15 and 29 from baseline.
    - National Early Warning Score (NEWS):
        - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
        - Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS.
    - Oxygenation:
        - Oxygenation free days in the first 28 days (to day 29).
        - Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients
    - Mechanical Ventilation:
        - Ventilator free days in the first 28 days (to day 29).
        - Incidence and duration of new mechanical ventilation use during the trial.
    - Hospitalization
        - Duration of hospitalization (days).

      Time to discharge (days)
    - Mortality
        - 15-day mortality.
        - 28-day mortality.

Exploratory objectives:

- To investigate the effects of NP-120 (20 and 40 mg TID) on lung function, health status, and SARS-CoV-2 RNA status in hospitalized patients with COVID-19 disease.

Safety objectives:

- To study the safety of NP-120 (20 and 40 mg TID) in hospitalized patients with COVID-19 disease.

3.2 Endpoints

Primary efficacy endpoint:

Patient clinical status (on the WHO 7-point ordinal scale) at day 15 in IP versus control group patients

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
6. Hospitalized, on invasive mechanical ventilation or ECMO
7. Death

Secondary efficacy endpoints:

- Status on an ordinal scale assessed daily while hospitalized and on days 15 and 28 in IP versus control group patients
- NEWS assessed day 3, 5, 8 ,11 while hospitalized and on days 15 and 29 in IP versus control group patients
- Rate of mechanical ventilation in IP versus control group patients
- Duration of mechanical ventilation (if applicable) in IP versus control group patients
- Duration of supplemental oxygen in IP versus control group patients
- Time to return to room pressure (SpO2 > 94%)
- Duration in ICU (if applicable) in IP versus control group patients
- Rate of Mortality in IP versus control group patients
- Duration of hospitalization in IP versus control group patients
- Time to discharge in IP versus control group patients
- Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients

Secondary safety endpoints:

The following safety parameters will be evaluated for the duration of the study:

- Type, frequency, severity, and relationship of AEs to investigational product (IP).
- Number of patients who discontinue IP due to any AE.
- Frequency of clinically significant changes in vital signs and/or laboratory findings.

Exploratory efficacy endpoints:

- Changes in the extent of dyspnea from baseline, using a Likert scale, at Days 2, 4, 8, and 14 in IP versus control group. [Likert scale: The patient grades his/her current breathing compared to when he/she first started the IP (from -3 to 3). "0" = no change, "1" =minimally better, "2" =moderately better, "3" =markedly better, "-1" =minimally worse, "-2" =moderately worse, "-3" =markedly worse]. For the first questionnaire (at baseline), the patient compares their current shortness of breath to their shortness of breath when they are well.
- Rate of change to patient's experience of cough (Visual analog scale [VAS]) at Days 2, 4, 8, and 14 in IP versus control group. VAS: The patient draws a vertical line on an axial graph (from 0 to 100) to show the degree of how he/she feels about coughing. The number "100" equals the worst

coughing the patient has ever felt and the number "0" equals the best he/she has felt since baseline.

- Changes in D-dimer in IP versus control group
- Qualitative PCR for SARS-CoV-2 at baseline, days 5 (while hospitalized, and days 15 and 29 (if able to return to clinic or still hospitalized)
- Quantitative PCR (if available) for SARS-CoV-2 at baseline, days 5 (while hospitalized, and days 15 and 29 (if able to return to clinic or still hospitalized)

4. STUDY DESIGN

4.1 Overall Design

This is a Phase 2b/3, multicenter, open label, randomized, parallel group study to evaluate the efficacy of Ifenprodil in patients with COVID-19 disease.

In the Phase 2b phase, patients will be randomized in a ratio of 1:1:1 to either a) 20 mg TID IP plus Standard of Care group, b) 40 mg TID IP plus Standard of Care or c) Standard of Care only group. Investigators will collectively enroll approximately 50 evaluable patients in each treatment group, for a total of 150 patients. Patients receive either oral Ifenprodil (20 or 40 mg TID) for up to 14 days in addition to Standard of Care, or Standard of Care only. The Standard of Care for each patient will be captured in the eCRF.

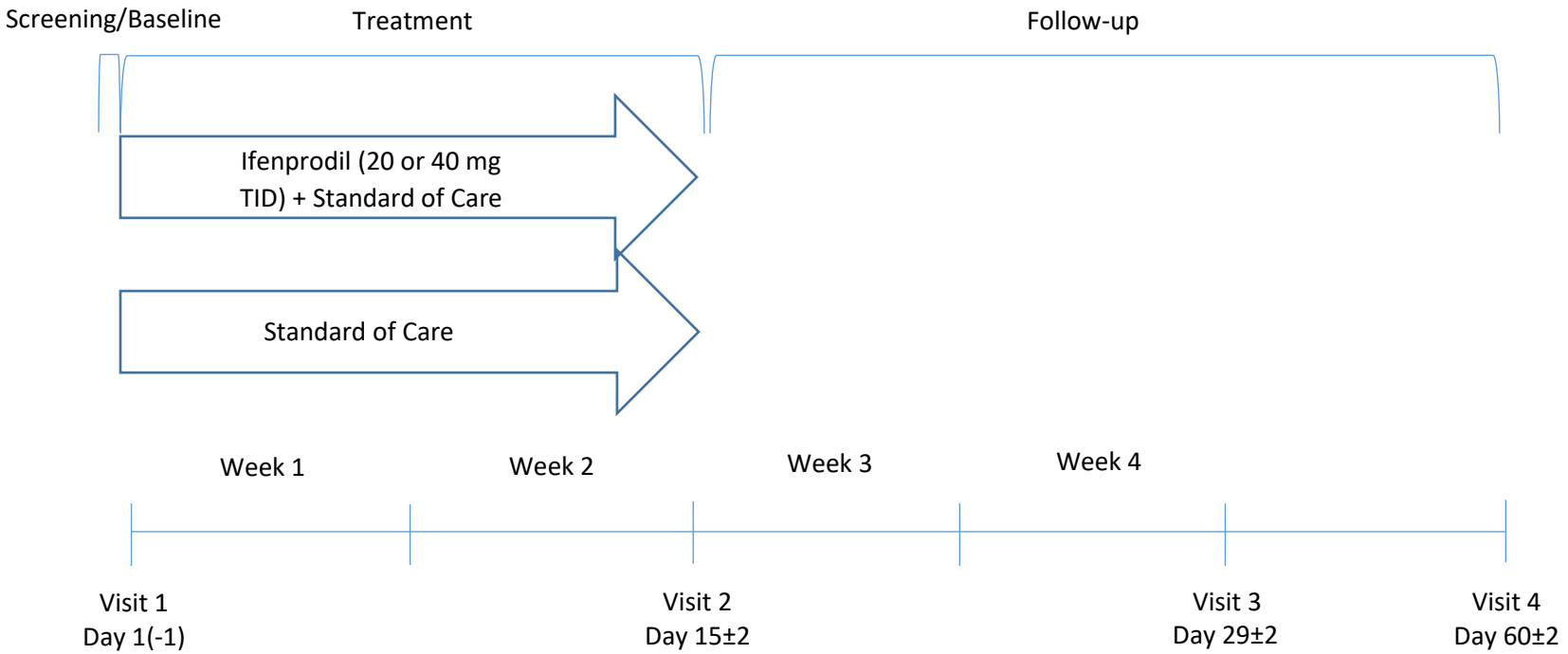
Randomization will be stratified by site, and age (<65 versus ≥65).

For Phase 2b, One interim statistical analysis will be performed on the primary endpoint of each arm after the first 75 patients have completed up to 2 weeks of treatment (Day 15). This analysis is being done to allow safety assessment and some snapshots of efficacy assessments as the trial progresses.

The Phase 2b study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Data from the Phase 2b study will be used to down select and prioritize the secondary endpoints. . The protocol would then be amended for the Phase 3 study to include the additional required number of patients to be recruited for the study to meet statistical significance in its primary endpoint.

An additional placebo arm will be added in the Phase 3 portion of the study. The number of participants to be enrolled in Phase 3 pivotal stage will be determined based upon the outcome of pilot Phase 2b stage of the study. Participants will be randomized to receive IP plus SOC, or Placebo plus SOC. Details will be outlined in a protocol amendment

Figure 3 Overview of Trial Design



4.2 Planned Number of Patients

In total, approximately 682 patients with COVID-19 disease at sites in Canada, the US, Australia, the Philippines, and Romania will be enrolled competitively. Addition countries may be added depending on enrolment. Adjustments to sample size may be made depending on the results of the final analysis from Phase2b.

4.3 Data Safety Monitoring Board

An Independent Data and Safety Monitoring Board (DSMB) will be established. The DSMB is an expert advisory group commissioned and charged with the responsibility of evaluating, primarily, cumulative safety data at regular intervals. The DSMB will review blinded data and provide recommendations to the Sponsor based on their evaluation. All DSMB members will be independent of the Sponsor and study. Membership in the independent DSMB will consist of at least a medical monitor, a physician, a statistician, and a pharmacologist. All members have experience and expertise in their field of practice, and will not have scientific, financial or conflict of interest related to the trial.

A DSMB Charter will be prepared and signed prior to initiation of the first DSMB meeting. The charter will outline the specific purpose and functions of the DSMB in monitoring the safety of patients in the trial. This charter will also describe the procedures for data extraction and data delivery conventions to and from the DSMB members for review purposes, and decision criteria to recommend changes to study parameters like the primary endpoint, eligibility requirements, and sample size.

The first DSMB meeting to review safety data, other than the orientation meeting, will occur when 25 subjects have completed Visit 2 (Day 15) of the study. A subsequent DSMB meeting will occur after each 25 subjects have completed Visit 2 (Day 15) up to 100 subjects; subsequent to 100 subjects, review will occur after every 50 subjects have completed Visit 2 (Day 15). The study will not stop enrolment awaiting these DSMB reviews, although the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews.

Should initial enrollment be slower than expected, the DSMB will have the option of reviewing data prior to the 25 subject/Visit 2 event if the DSMB believes such a review would be of value. An earlier review would be in addition to the planned 25 subject/Visit 2 review. Should any untoward safety issue be observed, the DSMB will schedule an immediate meeting to review the relevant safety data.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the DSMB. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the AEs in an unblinded fashion and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this trial.

4.4 Design Justification

This study represents one of the first repurposed investigations of Ifenprodil in patients with COVID-19 disease. This study will provide information on the safety and clinical efficacy in the SARS-CoV-2 infected population prior to advancing to larger clinical trials, as well as provide critical information for the design of future studies in this population.

The purpose of this study is to determine whether Ifenprodil is effective and safe in the treatment of patients with COVID-19 disease. The primary measure of efficacy will be patient clinical status (on a 7-point ordinal scale) at day 15 in IP versus control group patients. This protocol is based on the recommendations of the WHO R&D Blueprint Clinical Trials Expert Group.

The Phase 2b stage will be an open label study with patients, investigator, site and CRO staff aware of treatment received. The Phase 3 stage of the protocol will also include a placebo arm to allow for double-blinding.

4.5 Dose Justification

20 mg TID:

20 mg TID of Ifenprodil is within the recommended dosing guidelines for other indications as per the manufacturer's package insert.

Assuming a 60 kg person, a single 20 mg dose would yield a 0.333 mg/kg weight adjusted dose. To convert to a mouse dose, a factor of 12 is applied to the human equivalent dose (Nair and Jacob, 2016), which results in approximately 4 mg/kg for mice.

A 4 mg/kg dose given three times daily (12 mg/kg total daily dose) was found to be efficacious in reducing pulmonary fibrosis, and better than a single 30 mg/kg daily dose in reducing fibrosis in mice. The independent study involving H5N1 infection in mice also used a single daily dose of 20 mg/kg.

Similarly, the single 1.5 mg/kg dose selected in the acute cough model in the guinea pig was also equivalent to the single 20 mg/kg human dose on a body surface area adjusted basis based on an adjustment factor of 4.6.

Thus, the current 20 mg TID human dose is proposed to be a reasonable dose for this initial exploratory study. Please refer to the Investigator's Brochure for additional details on the aforementioned pre-clinical studies.

40 mg TID:

40 mg TID of Ifenprodil is also expected to be a reasonable dose for this exploratory study. Long term pre-clinical toxicological studies suggest dosing up to 16 mg/kg/day should produce no adverse effects. Specifically, the no-observed-adverse-effect level (NOAEL) observed were 50 mg/kg/day (HED of 8 mg/kg/day) in repeat oral dose studies in the rat of up to 52 weeks (Kawai et al, 1975a; Kawai et al, 197b), 30 mg/kg day (HED of 17 mg/kg/day) in dogs of up to 6 months (Nagata et al, 1997), and 50 mg/kg/day (HED 16 mg/kg/day) in rabbit of 30 days (Kawai et al, 1976).

Furthermore, high doses of Ifenprodil (60-300 mg/day) have been used for analgesic purposes in humans. In addition, a trial using 120 mg/day of Ifenprodil for methamphetamine dependence is underway in Japan (UMIM clinical trial registry UMIN000030849; Kotajima-Murakami et al, 2019) for 84 days. Assuming a 60 kg subject, the proposed 40 mg TID dose in this study is 2 mg/kg/day dose level and limited to 14 days exposure, well within previously used dosing regimens.

4.6 Trial Schedule and End-of-Trial

First patient first visit is planned for the Third Quarter of 2020 and last patient last visit is planned for the First Quarter 2022. The expected total duration of the trial is approximately 18 months.

The End of Trial is defined as the date of the last visit of the last patient to complete the study.

At the end of the trial patients will be treated for their COVID-19 disease at the discretion of the Investigator.

4.7 Trial Stopping Rules and Safety

The Medical Monitor will review AE / SAE data every 2 weeks. If there are a concerning number of unexpected AEs, the DSMB will be asked to review safety data in an ad hoc meeting.

The DSMB will review safety data after every 25 subjects are entered into the trial up to 100 subjects, and then at every 50 subjects; ad hoc reviews will be undertaken if there are other specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews. Following the recommendations of the of the WHO R&D Blueprint Clinical Trials Expert Group and given the severity of illness in COVID-19, there are no pre-specified study stopping rules for safety.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1 Inclusion Criteria

1. Male and female subjects aged ≥18 years of age
2. Confirmed coronavirus infection
    a) Positive real-time fluorescence polymerase chain reaction of the patient's respiratory or blood specimens for SARS-CoV-2 nucleic acid
    b) Viral gene sequences in respiratory or blood specimens that are highly homologous to SARS-CoV-2
    c) Any other diagnostic test accepted by local regulatory authorities
3. Must be hospitalized and requiring supplemental oxygen, or on non-invasive ventilation or high flow oxygen devices (Score of 4 or 5 on WHO Ordinal Clinical Scale)
4. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (e.g. oral contraceptives, intrauterine device, diaphragm plus spermicide) from the time of screening and must agree to continue using such precautions for 90 days after the final dose of study drug(s)

5. Non-sterilized males who are sexually active with a female partner of childbearing potential must use condom plus spermicide from day 1 through 90 days after receipt of the last dose of study drug(s)
6. Subjects (or legal designate) must have the capacity to understand, sign and date a written, informed consent form and any required authorization prior to initiation of any study procedures

5.2 Exclusion Criteria

1. Patients with vasodilatory shock, orthostatic hypotension, hypotension, or tachycardia at screening/baseline
2. Patients experiencing cerebral hemorrhage or cerebral infarction at baseline
3. ALT/AST > 5 times the upper limit of normal; Child-Pugh Score 10 to 15.
4. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
5. Patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
6. Patients taking droxidopa
7. Pregnant and lactating women and those planning to get pregnant
8. Known or suspected allergy to the trial drug or the relevant drugs given in the trial
9. Presence of other disease that may interfere with testing procedures or in the judgement of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial
10. Know inability of patient to comply with the protocol for the duration of the study
11. Involvement in a clinical research study within 4 weeks prior to screening and/or prior enrollment in the study or plan to participate in another interventional clinical trial during the study period. Participation in observational registry studies is permitted.

5.3 Screening/Baseline/Randomization

Screen failures are defined as patients who consent to participate in the clinical trial but are never subsequently enrolled. In this study, a patient can become a screen failure at any time during the screening visit (Visit 1), prior to randomization. In order to ensure transparent reporting of screen failure patients, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, and Eligibility Criteria.

When a patient meets all eligibility requirements, study site personnel will consult the study database to obtain the patient's randomization number and treatment assignment.

Under no circumstances will patients randomized in the trial be permitted to be re-screened and randomized for a second time in this trial.

5.4 Premature Withdrawal and Discontinuation Criteria

5.4.1 Withdrawal from Randomized Treatment or from the Study by Patient

The patients have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the Investigator should record the reason for the patient's withdrawal, if

possible. Every effort should be made to encourage patients to remain in the study for the duration of their planned outcome assessment.

In case the patient has withdrawn consent, no new data can be entered into the e-CRF and data will be recorded in the medical records only. Correction of previous data entries and/or entering of data related to visits/procedures done prior to but made available after withdrawal of consent (e.g. laboratory results) will be allowed unless the patient disapproves it.

5.4.2 Discontinuation of Study Drug

A patient in this clinical study may discontinue study drug for any of the following reasons:

- An adverse event which, in the opinion of the Investigator necessitates withdrawal of study drug
- A patient's substantial non-compliance (e.g. visits non-compliance)
- The Investigator's opinion that continuing the patient in the trial is not appropriate. The Investigator may withdraw a patient at any time if it is considered to be in the patient's best interest.
- Patient requests to discontinue study drug
- Patients who suffer vasodilative shock. However, physicians can use rescue therapy such as vasopressin to restore blood pressure and allow patients to continue in the study, at the discretion of the attending physician.
- Patients whose ALT/AST rise to >5x upper limit of normal or Child Pugh score of 10-15.
- Patients who experience a cerebral hemorrhage or cerebral infarction

Patients discontinued from study treatment should remain in the study and complete all remaining study assessments. If not possible, at a minimum, they should be invited to a Safety Follow-up Visit 7 days after the last dose of IP as soon as possible after a decision of discontinuation has been taken. At these visits, the Investigator will obtain all the required details and document the date of the premature termination and the main reason in the e-CRF. If the reason for study drug discontinuation is an adverse event, the specific event will be recorded in the e-CRF.

NOTE: patients that progress to mechanical ventilation during the study may remain on study drug and should not be withdrawn.

Definition of Dose Limiting Toxicity:

The occurrence of any of the following toxicities from the initial dose of Ifenprodil administration (in combination with Standard of Care (SOC)) which results in:

a. The necessity to delay ifenprodil administration in the participant, OR

b. To reduce the dose of ifenprodil administered, either for the participant, or for subsequent participants,

will be considered a DLT, if judged by the investigator to have a reasonable possibility of being related to the ifenprodil administration.

Severity is graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 equivalents of mild, moderate or severe:

1. Grade 3 or higher toxicity, except elevations in gamma-glutamyltransferase (GGT)

2. Grade ≥ 3 AST/ALT elevation

3. Grade ≥ 2 AST/ALT elevation with Grade ≥ 2 bilirubin elevation

5.4.3 Withdrawal of Patients from the Study

The Investigator also has the right to withdraw patients from the study post initial dosing. Whenever possible the patient should be followed for all assessments per protocol. Patients will be withdrawn in the following circumstances:

- Patients withdraws consent or requests discontinuation from the study for any reason
- Death of the patient
- Termination of the study
- Loss to follow-up (every effort must be made to contact the patient; phone calls on three separate days must be made, and a certified letter must be sent to the patient's most recent address)

Any withdrawal must be fully documented in the e-CRF and source documents, registered in the e-CRF as discontinued, and followed by the Investigator/Investigative Staff. Patients who withdraw from the study or are lost to follow-up after signing the informed consent form and randomization will not be replaced.

5.5 Rescue Medication and Risk Management Plans

Cautions from the manufacturer of Ifenprodil include monitoring for hypotension, palpitations/increased heart rate, and risk of bleeding (including those patients on drugs with a risk of bleeding). Investigators should monitor their patients for occurrence of these adverse events and proceed as follows:

Vasopressin can be used as a rescue therapy for patients who suffer vasodilative shock. If low blood pressure occurs, use of vasopressor medication may also be considered. This may or may be coincident with an increased heart rate, in which case a vasopressor may correct both events. In the event of an increased heart rate in the absence of coincident hypotension, use of a positive inotropic agent may be considered. In the event of an increased risk of bleeding, antifibrinolytic therapy may be considered. Please consult with the Medical Monitor regarding the best course of treatment should any of these events occur.

In addition, patients should be monitored for elevation in liver enzymes. Those patients whose ALT/AST rise to >5x the upper limit of normal and/or Child Pugh score of 10-15 should be discontinued from study medication (ifenprodil). In addition, the Medical Monitor and DSMB will monitor for the occurrence of these adverse events as part of their normal safety review. Additional guidance or updates to the protocol will be provided if necessary.

The DSMB will review the adverse events profile after 25, 50, 75 and 100 patients enrolled in the study, then every 50 patients thereafter. Particular attention will also be paid to patients over 65 for the frequency and severity of serious adverse events (e.g. ALT/AST, creatinine) as the manufacturer has mentioned caution should be taken in this particular age group. If, based on the DSMB's opinion, there is a significant concern in any of the identified risk groups, additional restrictions may be added to the inclusion/exclusion criteria.

5.6 Appropriate Methods of Contraception for Study

Females of childbearing potential: Women who are sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception, such as oral contraceptives, intrauterine

device, or diaphragm plus spermicide from the time of screening and must agree to continue using such precautions for 90 days after the final dose of study drug(s)

Non-sterilized males: Men who are sexually active with a female partner of childbearing potential must use condom plus spermicide from day 1 through 90 days after receipt of the last dose of study drug(s)

6. STUDY TREATMENT

6.1 Description of the Investigational Product

The chemical name of Ifenprodil tartrate is (1RS,2SR)-4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl] phenol hemi-(2R,3R)-tartrate. The drug is more commonly referred to as ifenprodil. Ifenprodil will be provided as white, round, biconvex, film-coated tablets containing 20 mg of the active ingredient. All IP is provided by the sponsor and is produced and handled according to the principles of Good Manufacturing Practice (GMP).

6.2 Treatment Administration and Schedule

Tablet/s (20 mg TID arm = 1 tablet; 40 mg TID arm = 2 tablets) will be taken by mouth TID after food (if possible) in the in the morning (AM, upon rising), in the afternoon (PM, 6-10 hours following first dose), and evening (PM, 6-10 hours before the next day's anticipated first dose). Best efforts should be made to keep the three doses approximately 8 hours apart. The length of dosing for the study is up to 2 weeks (either to hospital discharge, or Day 14, whichever comes first).

The first dose of study medication will be taken on day 1 at the first visit, following randomization.

In cases where the patient is unable to swallow tablets the use of a nasogastric/stomach tube is permitted. Crushing and administration of tablets should follow local practices/SOPs.

Study drug administration should continue until the end of Day 14, or hospital discharge, whichever comes first.

6.3 Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

Description of Product: White, round, biconvex, film-coated tablets containing 20 mg of the active ingredient.

Investigational Drug Packaging and Labeling: The study drug (Ifenprodil) will be supplied by Algernon Pharmaceuticals, in cartons containing blister packs (50 tablets contained in 5blister packs (10 tablets per blister pack)).

The study drug will be provided to the sites by Algernon Pharmaceuticals. Separate labels, as per the GMP regulations and requirements will also be provided for site staff to apply to the packages and blister packs, as provided by the local laws. All investigational labels for the study drug will meet applicable country specific regulatory requirements.

Storage: Store in a dry dark place at temperatures no higher than 25°C, keep protected from moisture.

Dispensing: Study treatment must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the study treatment will be limited to the investigator and authorized site staff.

Drug Return/Destruction: The clinical site, upon confirmation with Sponsor, should follow their local regulations for final disposition of unused study treatment.

6.4 Accountability

Only patients enrolled in the study may receive study treatment.

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). Study treatment must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the study treatment will be limited to the investigator and authorized site staff.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction, including responsibilities for the site versus the Sponsor (or designee). Further details can be found in the Pharmacy Manual.

6.5 Compliance with Study Treatment Administration

Study personnel will review the instructions printed on the package with the study patients prior to dispensing the IP. The IP will be dispensed as noted in Table 3.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 Informed Consent

Voluntary written informed consent must be obtained before any study-related procedures are performed in accordance with the International Conference on Harmonization (ICH) E6 Guidelines for Good Clinical Practise (GCP) and the regulatory requirements of informed consent for each jurisdiction (e.g. US Title 21 Code of Federal Regulations (CFR) Part 50, Canadian Food and Drug Regulations, Part C Division 5). Consent must be documented by the use of a written consent form approved by Algernon Pharmaceuticals and the IEC/IRB. A copy of the signed informed consent will be provided to the patient/parent/guardian/legal representative signing the form and the original retained in the source documents of the study participant. Documentation of the consent process must be collected with the source documents at the site.

7.2 Trial Flowchart

The trial includes a Screening/Baseline visit, a 2-week open label Treatment Period, and a 6-week Safety Follow-up Period to Day 60. All periods are associated with evaluations and procedures that must be performed at specific time points, as described in Section 7.3. The Schedule of Events (Table 3) summarises the frequency and timing of trial events.

Table 3 Schedule of Events

Trial Activity	Screening/Baseline/ Enrolment visit	Daily until hospital discharge	End of treatment	Follow-up period	
Day	1	2-14	15	29	60
Allowed window for visit (±)	-1[a]		2	2	3
Visit	1		2[b]	3	4
Informed consent	●				
Inclusion/exclusion criteria including confirmation of COVID-19 diagnosis	●				
Confirmation SARS-CoV-2[h]	●	●	●	●	
Pregnancy test	●				
Demographics/Medical History	●				
Physical Exam	●				
Vital signs[c]	●	●	●	●	
Clinical support data collection[f]	●	●	●	●	
Safety Laboratory Testing[d]	●	●	●	●	
Cytokine Markers[k]	●	●	●		
Child-Pugh Score[i]	●	●			
PaO2 and PaO2/FiO2 ratio[j]	●	●	●	●	
ECG	●				
Cough Severity (VAS)[e]	●	●	●	●	
Extent of Dyspnea (Likert Scale)[e]	●	●	●	●	
Adverse Events documented	●	●	●	●	●
Concomitant Medications	●	●	●	●	
Randomization	●				
Administer IP	●	●			
Vital Status					●[g]

[a] Screening/baseline may occur up to 24 hours prior to randomization
[b] Treatment can be given up to 14 days post randomization, or until hospital discharge, whichever comes first. If patient is discharged prior to Day 14, the next visit should be Visit 2.
[c] Includes blood pressure (measured after the patient has been in a seated position (if possible) for ≥3 minutes of rest), pulse, respiratory rate, body temperature, and SpO2. Body weight and height will be measured at the screening visit only.

[d] Baseline, Days 3, 5, 8, 11 if hospitalized, Day 15, Day 29
[e] Baseline, Days 2, 4, 8, and 14 if hospitalized, Day 15 (if not done Day 14), Day 29
[f] Includes NEW Score, on Baseline, Days 3, 5, 8, 11 if hospitalized, Day 15, Day 29
[g] Vital status (is patient alive)
[h] Baseline, Days 5 (or discharge, whichever comes first) and 15. Day 29 for subjects with viral RNA detected at Day 15. Qualitative (mandatory) and Quantitative (if available) testing done all days.
[i] Baseline, Days 3, 5, 8, 11 if hospitalized
[j] Minimum complete baseline, Days 3, 5, 8, 11, 15 and 29. If PaO2 not able to be taken, SpO2 should be obtained using a forehead sensor. Fingertip probes may be used if forehead sensors are not available. Remain consistent with the method of testing for the patient over the course of the study.
[k] Cytokine markers at Baseline, Day 5, Day 15 (if available per local lab): IFN-γ, GM-CSF, IL-6, IL-12, TNF-α

7.3 Visits

7.3.1 Visit 1 (Screening/Baseline/Enrollment)

At Visit 1, information will be collected for evaluation of trial eligibility by provided information as follows and patients will be randomized and dosed after confirmation of eligibility:

- Signing ICF (prior to any trial-related activities)
- Inclusion criteria and exclusion criteria
- Demographics (gender, date of birth, race and ethnic origin) and relevant medical and surgical history
- Confirmation of COVID-19 diagnosis (SARS-CoV-2 RNA confirmation). Include dates of onset of symptoms (if available) and initiation of treatment.
- Pregnancy test (females of reproductive age; Romania: Serum beta-human chorionic gonadotropin [β-HCG]; Rest of World: Serum beta-human chorionic gonadotropin [β-HCG] or urine test is acceptable)
- Vital signs measurements (including pulse, respiration rate, body temperature, systolic and diastolic blood pressure measured with the patient in a seated position [if possible] after ≥3 minutes of rest), and SpO2. Body weight and height will be included for the screening visit only
- Limited Physical Exam
- Assess baseline measures of clinical support
    - Hospitalized
    - Oxygen requirement
    - Non-invasive mechanical ventilation (via mask)
    - Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
    - ECMO requirement
    - Ordinal Scale Assessment
        1. Not hospitalized, no limitations on activities
        2. Not hospitalized, limitation on activities
        3. Hospitalized, not requiring supplemental oxygen
        4. Hospitalized, requiring supplemental oxygen
        5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
        6. Hospitalized, on invasive mechanical ventilation or ECMO
        7. Death
    - For the purposes of eligibility/baseline the worse score from the previous day (Day -1) will be used
    - NEW Score
- Safety laboratory testing
- Child-Pugh Score
- Cytokine Markers
- PaO2 and PaO2/FiO2 ratio
- ECG
- VAS (if possible)
- Extent of Dyspnea (if possible). For the first questionnaire (at baseline), the patient compares their current shortness of breath to their shortness of breath when they are well.)
- Concomitant medications documented
- Randomization* after eligibility confirmation. All screening/baseline procedures must be completed prior to randomization and administration of study medication.

- Begin administration of study medication after randomization (within 24 hours of screening procedures).

*Randomization should occur within 24 hours of screening procedures.

7.3.2 Daily Assessments (Days 2 - 14; Treatment Period)

At each study day while hospitalized, the following data will be collected:

- Vital signs (including pulse, respirations rate, body temperature, systolic and diastolic blood pressure, SpO2)
- Assess measures of clinical support
    - Hospitalized
    - Oxygen requirement
    - Non-invasive mechanical ventilation (via mask)
    - Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
    - ECMO requirement
    - Ordinal Scale Assessment
    - The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2. The scale is as follows:
        1. Not hospitalized, no limitations on activities
        2. Not hospitalized, limitation on activities
        3. Hospitalized, not requiring supplemental oxygen
        4. Hospitalized, requiring supplemental oxygen
        5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
        6. Hospitalized, on invasive mechanical ventilation or ECMO
        7. Death
    - NEW Score (Days 3, 5, 8 ,11 if still hospitalized)
- SARS-CoV-2 RNA status testing (Day 5, or discharge, whichever comes first)
- Safety laboratory testing (Days 3, 5, 8, 11 if still hospitalized)
- Child-Pugh Score (Days 3, 5, 8, 11 if still hospitalized)
- Cytokine Markers (Day 5)
- PaO2 and PaO2/FiO2 ratio
- VAS score questionnaire (Days 2, 4, 8, and 14 if still hospitalized)
- Extent of Dyspnea (Likert Scale, Days 2, 4, 8, and 14 if still hospitalized)
- Adverse Events recorded
- Concomitant medications
- IP administration (daily until discharge or Day 14)

7.3.3 Visit 2 (Day 15 ±2; End of Treatment Period)

During this visit the following data will be collected:

- Vital signs (including pulse, respirations rate, body temperature, systolic and diastolic blood pressure, SpO2)
- Assess measures of clinical support
    - Hospitalized
    - Oxygen requirement
    - Non-invasive mechanical ventilation (via mask)

  - Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
  - ECMO requirement
  - Ordinal Scale Assessment
    1. Not hospitalized, no limitations on activities
    2. Not hospitalized, limitation on activities
    3. Hospitalized, not requiring supplemental oxygen
    4. Hospitalized, requiring supplemental oxygen
    5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
    6. Hospitalized, on invasive mechanical ventilation or ECMO
    7. Death
  - NEW Score
- SARS-CoV-2 RNA status testing
- Cytokine Markers
- Safety laboratory Testing
- PaO2 and PaO2/FiO2 ratio
- VAS (if not performed on Day 14; if possible)
- Extent of Dyspnea (if not performed on Day 14; if possible)
- Adverse Events recorded
- Concomitant medications

It is understood that restrictions on the return of study patients to the clinical site may be in place after their discharge from hospital. If not possible for the patient to return, the site may use remote methods (for example Telehealth, remote or nurse for hire, remote laboratories) to obtain the visit specific measurements/samples for both Visits 2 (Day 15; End of Treatment) and 3 (Day 29; Safety Follow Up Visit).

7.3.4 Visit 3 (Day 29 ±2; Safety Follow Up Visit)

For all continuing patients, a Safety Follow-up Visit will be scheduled on Day 29 (Week 4). For patients that have discontinued from the study, they will be invited to attend a Safety Follow up visit 7 days after their last dose of IP and following the same schedule of events as Visit 3.

The following data will be collected:

- Vital signs (including pulse, respirations rate, body temperature, systolic and diastolic blood pressure, SpO2)
- Assess measures of clinical support
  - Hospitalized
  - Oxygen requirement
  - Non-invasive mechanical ventilation (via mask)
  - Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
  - ECMO requirement
  - Ordinal Scale Assessment
    8. Not hospitalized, no limitations on activities
    9. Not hospitalized, limitation on activities
    10. Hospitalized, not requiring supplemental oxygen
    11. Hospitalized, requiring supplemental oxygen
    12. Hospitalized, on non-invasive ventilation or high flow oxygen devices
    13. Hospitalized, on invasive mechanical ventilation or ECMO

14. Death
    - NEW Score
- SARS-CoV-2 RNA status testing (if still positive on Day 15)
- Safety laboratory Testing
- PaO2 and PaO2/FiO2 ratio
- VAS (if possible)
- Extent of Dyspnea (if possible)
- Adverse Events recorded
- Concomitant medications

7.3.5 Visit 4 (Day 60±2; Vital Status Follow Up Visit)

At the Safety Follow-up Visit, the following data will be collected:

- Vital Status (alive, deceased)
- Adverse Events recorded

Note: This visit may be conducted via phone call.

7.4 Assessments

7.4.1 Vital Signs

Vital signs will be measured as indicated in Section 7.3 and Table 3 and will include blood pressure (measured after the patient has been in a seated position, if possible, for ≥3 minutes of rest), pulse, respiration rate, body temperature, SpO2, and weight and height (screening visit only). Standard of care measurements can be used if they fall within the protocol specific windows.

The Investigator should evaluate the clinical significance of the results. Clinically significant abnormal findings will be reported as adverse events.

7.4.2 Safety Laboratory Parameters

Samples for laboratory analysis in local laboratories will be collected during the study at time point specified in the schedule of events (See Table 3 and Section 7.3). All safety laboratory tests will be analyzed at the local laboratory, unless specified in the protocol. Standard of care measurements can be used if they fall within the protocol specific windows.

The Investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are non-clinically significant or clinically significant. Pre-existing clinically significant conditions diagnosed as a result of the screening procedures must be recorded as medical history. If any clinically significant abnormal findings are discovered after informed consent or any pre-existing conditions worsen during the trial, these must be recorded as adverse events. The laboratory report will be signed and dated by the Investigator.

7.4.2.1 Hematology

Hemoglobin, hematocrit, white blood cell counts, including differential, platelet count, red blood cell count, myoglobin

7.4.2.2 Chemistry

Glucose, blood urea nitrogen (BUN), serum creatinine, sodium, potassium, chloride, bicarbonate, ALT, AST, GGT, alkaline phosphatase, total bilirubin, calcium, phosphorus, albumin, total protein, uric acid

7.4.2.3 Coagulation

APTT, PT, INR, D-dimer.

7.4.2.4 Urinalysis

Specific gravity, hydrogen ion concentration (pH), protein, glucose, bilirubin, ketone, urobilinogen, blood, leukocytes, casts, bacteria.

7.4.3 Cytokine Markers

The following cytokines should be collected if available at local laboratory: IFN-γ, GM-CSF, IL-6, IL-12, TNF-α

Cytokine markers to be collected at Baseline, Day 5, Day 15.

7.4.4 Clinical support status

Patients will be assessed for their measures of clinical support, including:

- Hospitalized
- Oxygen requirement
- Non-invasive mechanical ventilation (via mask)
- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
- ECMO requirement
- Ordinal Scale Assessment
    - The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2.
    - For the purposes of baseline the worse score from the previous day (Day -1) will be used
    - The scale is as follows:
        1. Not hospitalized, no limitations on activities
        2. Not hospitalized, limitation on activities
        3. Hospitalized, not requiring supplemental oxygen
        4. Hospitalized, requiring supplemental oxygen
        5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
        6. Hospitalized, on invasive mechanical ventilation or ECMO
        7. Death

7.4.5 National Early Warning Score (NEWS)

The NEW score has demonstrated an ability to discriminate patients at risk of poor outcomes (WHO R&D Blueprint Master Protocol; Royal College of Physicians 2012 and 2017). This score is based on 7 clinical parameters. The NEW Score is being used as an efficacy measure.

This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. i.e. on Day 3, Day 3 score is obtained and recorded as Day 3.

A copy of the Table for determining NEW Score can be found in Appendix 16.1.

7.4.6 Demography
Demographic data will be collected at the Screening Visit, including gender, date of birth, race, and ethnic origin (to the extent allowed by local regulations).

7.4.7 Medical and Surgical History
Information on clinically significant previous and concomitant illnesses, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the Screening Visit will be recorded as medical and surgical history at Screening. For planned procedures/hospitalisations during the trial, documentation should be completed at the time of the Screening.

7.4.8 Physical Exam
A limited physical examination will be performed at screening.

Assessments for the physical examination should include those systems affected by the SARS-CoV-2 infection. These can include: General appearance, Eyes, Ears/Nose/Throat, Respiratory (Chest/Pulmonary), Heart, Abdomen, Vascular, Neurological, Musculoskeletal, Lymphatic (Lymph nodes), Skin.

Standard of care measurements can be used if they fall within the protocol specific windows.

If during routine clinical care during the study the physician notes any physical findings of interest these should be noted in the eCRF.

7.4.9 Prior and Concomitant Therapies
All medications (prescription and non-prescription), treatments, and therapies taken by the patient from screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the patient's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, date the medication was started, and date the medication was stopped (if not ongoing) must be recorded.

All Investigational COVID-19 therapeutic agents used both prior to, and current to randomization and participation in the study should be captured in the CRF.

7.4.10 Lung Function Test
Lung function will be assessed by PaO2 and PaO2/FiO2 ratio analyses, and two patient questionnaires. These assessments should be completed following the time points specified in the schedule of events (See Table 3 and Section 7.3). Standard of care measurements can be used for PaO2 and PaO2/FiO2 ratio analyses if they fall within the protocol specific windows.

7.4.10.1 PaO2 and PaO2/FiO2 Measurement Considerations
It is recognized that the performing of PaO2 and PaO2/FiO2 measurements can cause significant discomfort to patients. All efforts should be made in obtaining each PaO2 sample as per protocol. However, if not possible (e.g. patient refuses) at a minimum complete PaO2 measurements at baseline, Days 3, 5, 8, 11, 15 and 29.

For those days where PaO2 measurements are not able to be taken, SpO2 should be obtained. First preference is for these measurements to be taken using a forehead sensor. Fingertip probes may be used if forehead sensors are not available. The site should remain consistent with the

method of testing for the patient over the course of the study, e.g. all SpO2 measurements are taken with only forehead sensors.

7.4.10.1 Extent of Dyspnea (Likert scale)

The patient should grade his current breathing compared to when he first started the study (from -3 to 3). "0" = no change, "1" =minimally better, "2" =moderately better, "3" =markedly better, "-1" =minimally worse, "-2" =moderately worse, "-3" =markedly worse

For the first questionnaire (at baseline), the patient compares their current shortness of breath to their shortness of breath when they are well.

A copy of the Extent of Dyspnea (Likert Scale) can be found in Appendix 16.2.

7.4.10.2 VAS Questionnaire

Cough severity will be measured using a 0-100mm Visual Analog Scale (VAS) from "no cough" to "worst cough ever."

A copy of the VAS Questionnaire can be found in Appendix 16.3.

Note: the site should hand out the Visual Analogue Scale (VAS) to the subject for completion. If this is not possible, any alternative administration of the VAS must be documented clearly in the source. Reasons for an alternative method may include e.g. site policy to avoid document contamination, or a visually impaired subject. The following alternative options are accepted:

- Subject pointing to the VAS with some device and another person adding the line for them.
- If this is not possible, the subject can rank the score 0 – 100 (as the VAS line is 100mm). Site should hold up the VAS in front of the subject and/or describing this to try and retain some visual aspect.

7.4.11 Prohibited Therapy

Patient should not be taking droxidopa. Single use of ketamine is permitted. Use of unapproved/off label medications for COVID-19 treatment is permitted if they fall under the established local standard of care.

7.4.12 Safety Evaluations

Adverse events reporting, including clinically significant laboratory abnormalities, physical examinations and vital signs. AE event collection will be performed from signing of ICF, until end of study.

7.4.13 SARS-CoV-2 RNA Testing

Confirmation of SARS-CoV-2 RNA using one of the methods outlined in the Inclusion criteria should be performed at baseline, Day 5 (or at discharge if sooner), and at Day 15. Additional testing should be done at Day 29 if the patient still has detectable viral RNA at Day 15.

If possible, testing should be done using both qualitative (e.g. positive/negative) and quantitative (e.g. viral RNA load) methods, but at a minimum qualitative testing should be used. The route of testing (nasopharyngeal, oropharyngeal, blood, etc.) should be captured in the CRF.

8. ADVERSE EVENTS

8.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events MEETING the definition of an AE include the following:

- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition
- Any abnormal laboratory test results (urinalysis, haematology, or clinical chemistry) or other safety assessments (e.g. ECGs, vital signs measurements), including those that worsen from baseline, and are felt to be clinically significant in the medical and scientific judgement of the investigator
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures
- Overdoses and medication errors of the IP or concomitant medication with and without clinical consequences

Events NOT meeting the definition of an AE include the following:

- The disease being studied or expected progression, signs, or symptoms of the disease being studied, unless judged by the investigator to be more severe than expected for the patient's condition
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless more severe than expected for the patient's condition
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

8.1.1 Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAE) are undesirable events do not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment up to and including the follow up period.

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Treatment Emergent Adverse Events

The Investigator must monitor the condition of the patient throughout the trial from signing the ICF until the last visit.

The sources of treatment emergent adverse events cover:

- The patient's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the patient.

- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
- Other information relating to the patient's health becoming known to the Investigator (e.g. hospitalisation).

When an TEAE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an TEAE/SAE in the e-CRF. It is not acceptable for the investigator to send photocopies of the patient's medical records in lieu of completion of the TEAE/SAE e-CRF page.

8.2.2 Reporting of Treatment Emergent Adverse Events

A qualified Investigator will evaluate all TEAEs as to:

8.2.2.1 Adverse Event

- Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.
- If a patient suffers from the same adverse event more than once and the patient recovers in between the events, the adverse events should be recorded separately.
- Note the following: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalisation is not an adverse event; the reason for hospitalisation is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

8.2.2.2 Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event and assign to one of the following categories (NCI CTCAE):

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Everyday activities minimally or not affected
- Intervention not indicated; no or minimal therapy required

Moderate

- Symptom(s) cause moderate discomfort
- Some interference with normal everyday activities
- Local or non-invasive intervention indicated; drug therapy may be required

Severe

- Symptoms causing severe discomfort/pain
- Inability to perform daily social and functional activities (e.g. absenteeism and/or bed rest)
- Symptoms requiring medical/surgical attention/intervention; drug therapy is required

- An event is categorized as "serious" when it meets one of the pre-defined criteria for seriousness; an event may be severe in intensity but be of relatively minor medical importance (e.g. a severe headache). An event that is categorized as severe will not be confused with an SAE.

Life Threatening

- Life threatening consequences
- Urgent intervention required

Death

8.2.2.3 Causality

The possibility of whether the IP caused the adverse event must be classified as one of the following:

Reasonable possibility

The term "reasonable possibility" conveys that there is evidence or argument to suggest a causal relationship between the IP and the adverse event, rather than to imply that a relationship cannot be ruled out. The adverse event may occur as part of the pharmacological action of the IP or may be unpredictable in its occurrence

No reasonable possibility

A causal relationship of the AE to IP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed as necessary and provided as additional information becomes available.

8.2.2.4 Duration

The investigator will record the start and stop dates of the event. The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken, or the examination was performed. For pre-existing clinically significant conditions (diagnosed or observed as a result of the screening procedures) becoming worse after IP administration, the date of onset is the date the worsening began. The date of outcome is the date the patient recovered or died, or that the disease condition worsened.

8.2.2.5 Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (i.e. discontinuation, interruption, or reduction of IP, as appropriate), and report if concomitant and/or additional treatments were given for the event.

8.2.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. The Investigator is responsible for following all SAEs until the event has resolved or has stabilized.

8.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of IP dose, or any other therapeutic intervention; or
- Is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the e-CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

8.4 Adverse Events of Special Interest

Adverse events of special interest include known side effects of Ifenprodil. Nausea, dry mouth, loss of appetite, heartburn, diarrhea, constipation, headache, dizziness, allergic reactions, and heart palpitations are known to occur in between 0.1 – 5% of patients. Elevated ALT/AST levels have been observed in <1% of patients.

8.5 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female patient or partner of a male patient must be reported immediately. The IP should be discontinued, and the patient withdrawn from the trial.

The Investigator will follow the female patient until completion of the pregnancy and collect the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal, the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event. All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported within 24 hours of the Investigator's knowledge of the event.

8.6 Serious Adverse Events

8.6.1 SAE Definition

An SAE is an adverse event at any dosage that:

- Results in death;
- Is life threatening (in the opinion of the Investigator, at the time of the event;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity/disability;

- Is a congenital anomaly/birth defect; or
- Is an important medical event

Important medical events are defined as those that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important.

8.6.2 Reporting of Treatment Emergent SAEs

In order to meet the requirements for expedited reporting of SAEs meeting specific requirements to applicable regulatory authorities and IRB/IEC, all SAEs, must be reported to the Sponsor within 24 hours from the time the site investigational team first become aware of the event using the appropriate method as outlined in the Safety Reporting Guidelines.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, and reported using the appropriate method as outlined in the Safety Reporting Guidelines.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the patient's medical records and in the eCRF.

A planned hospitalization will not be a requirement of SAE reporting.

The Investigator is required to ensure that the data on these forms is accurate and consistent.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the patient signs informed consent until 7 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that is suspected of being related to IP.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to the Investigator as soon as these become available.

Where required by local legislation, the Investigator is responsible for informing the IRB/IEC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file, including correspondence with the IRB/IEC.

8.7 Follow-up of Treatment Emergent Adverse Events and Serious Adverse Events

During the trial, the Investigator must follow-up on each adverse event until it is resolved or until the medical condition of the patient is stable.

After the patient's last visit, the Investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IP until it is resolved or until the medical condition of the patient is stable. The Sponsor's Safety Surveillance Contact will follow all SAEs with outcomes pending until the last subject enrolled has completed the study.

9. DATA HANDLING

9.1 Data and Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

9.2 Electronic Case Record Form

An e-CRF system provided by an independent third-party CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following the CRO's procedures, in accordance with regulatory and system requirements.

Data should be entered into the system timely after the patient has attended a visit or after the data become available, as applicable.

The Investigator will approve/authorise the e-CRF entries for each patient with an electronic signature which is equivalent to a handwritten signature.

The e-CRF system and the database will be hosted at the independent third party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at the Sponsor. The Investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO. The PDF-files will be stored on an appropriate electronic storage device and will be provided to the Investigator before access to the e-CRF is revoked.

Errors occurring in the e-CRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

9.3 Data Management

Data will be collected via e-CRF and entered into the clinical database per the CRO's standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

9.4 Records Retention

Essential documents must be retained by Canadian Investigators for a minimum of 25 years after conclusion of the clinical study. For other jurisdictions, essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents are listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify the Sponsor if he/she wishes to assign the essential documents to someone else, remove them to another location, or is unable to retain them for a specified period. The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

10.1 Overview

Key elements of the Statistical Analysis Plan (SAP) are outlined in this section. The comprehensive plan will be documented in a separate SAP.

10.2 Study Population Definitions

The analysis populations are:

- **Intent-to-Treat (ITT):** The ITT population consists of all enrolled patients assigned to receive treatment regardless of whether they took study drug or stopped active treatment to receive only SOC. Patients will be classified according to the treatment group to which they were randomized.
- **Per-Protocol (PP):** The PP population consists of all ITT patients who are not major protocol violators with regards to inclusion/exclusion criteria, investigational product compliance and concomitant medication instructions. Protocol violations that would exclude patients from the PP population will be defined and documented in the SAP prior to unblinding.
- **Safety:** The Safety population consists of all patients who received at least one dose of study drug. This population will be used for all assessments of safety and tolerability. Patients will be summarized according to actual dose of study drug taken.

10.3 Sample Size and Power Considerations

For the pilot Phase 2b phase, a sample of 150 patients (50 in Arm A, Arm B and SOC) will be recruited. To account for drop out of 10%, a total of 168 patients will be enrolled.

For the pivotal Phase 3 phase, A sample of 462 patients (231 in the SOC group and 231 in the active treatment group) achieves 90% power to detect a change in the log odds ratio of 0.5596 when the significance level (alpha) is 0.05 using a two-sided test. A log odds ratio of 0.5596 corresponds to an odds ratio of 1.75 comparing treatment to SOC. The sample size was estimated using the *Tests for Two Ordered Categorical Variables* module in PASS 14. To account for drop out of 10%, a total of 514 patients will be enrolled.

The sample size assumes that the distribution of patients on day 15 will be as shown in Table 2, which is scenario 4 in the WHO master protocol (2020) for enrolled patients with moderate to severe disease under an odds ratio of 1.75.

Interim analysis and increasing the sample size

An interim analysis during Phase 2b will be conducted on the ITT population when 75 patients complete the clinical status assessment at day 15 (the primary endpoint). Details of outputs for interim analyses in Phase 3 will be specified in a separate mock shell document. A preliminary full analysis report of 150 patients with up to Day 29 entered will also be presented.

The following design features will also be assessed for possible changes for Phase 3 during the second interim analysis and/or final analysis for Phase2b.

- Target population; eligibility criteria
- The choice of primary endpoint
- The need for seven categories in the outcome scale (versus fewer)
- The distribution of patients across the outcome scale at day 15
- The timing (day 15) of the primary endpoint

10.4 Statistical Methods

Complete details of the statistical analysis methods, including data conventions, will be provided in the SAP.

10.4.1 General Conventions

Results will be presented by treatment group.

A baseline value is defined as the most recent available value collected or derived prior to the first study drug administration. A change from baseline value is defined as the difference between a result at a post-baseline time point and the baseline value. A percent change from baseline is defined as the ratio of the change from baseline value relative to the baseline value expressed as a percentage.

In general, continuous variables will be summarized using descriptive statistics (e.g. arithmetic mean, standard deviation [SD], median, minimum and maximum), as well as change from baseline for each applicable scheduled time point, when appropriate. Categorical variables will be summarized by frequency and percent observed in each category and at each time point as applicable. 95% CI may also be performed for some selected key outcomes of interest.

10.5 Patient Disposition

Patient disposition (analysis population allocation, entered, discontinued along with primary reason for discontinuation, completed) will be summarized using frequency and percentage.

A summary of patients enrolled by site will be provided.

Analysis sets and Protocol violations/deviations will be summarized using frequency tabulations.

Patient disposition information will also be listed.

10.6 Background and Demographic Characteristics

Patients' age, height, weight, and other continuous demographic and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term. Analysis will be done using the safety set and listed.

10.7 Prior and Concomitant Medication

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) and are defined as all medications taken during study treatment (including day 1) up to and including the follow up period. The number and percentage of patients using at least one concomitant medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 4) and preferred name (ATC-level 2). These will be summarized under safety analysis set and listed.

10.8 Treatment Exposure and Compliance

Treatment exposure and study drug compliance will be summarized using descriptive statistics under ITT, PP and Safety populations and listed.

10.9 Efficacy

10.9.1 Primary Efficacy Analysis

The SOC and treatment arms under WHO7 ordinal scale will be compared with respect to the primary endpoint using proportional odds models (ordinal logistic regression) adjusted for site and age. Treatment will be compared to SOC by testing whether the common odds ratio differs from 1.0 at day 15 using two-sided tests at 2.5% level of significance under the ITT population set, followed by PP population set. All modeling assumptions will be verified.

Separate 95% CI and p-values will be computed across each of the ordinal scale between SOC and treatment arms for both ITT and PP population sets. Multiple comparison techniques (to be detailed in the SAP) will be employed to ensure type I error is controlled to 5% for these comparisons.

If, following the Phase 2b interim analysis or final analysis, the primary endpoint changes for Phase 3, details will be written in the SAP, and a protocol amendment will be created.

10.9.2 Secondary Efficacy Analyses

Time to events, like initiation of mechanical ventilation, death, or hospital/ICU discharge, will be summarized using the Kaplan-Meier method and analyzed using proportional hazards regression where appropriate. VAS cough score will be summarized descriptively. All secondary efficacy analyses will be analyzed using an appropriate 2-sided hypothesis test at 5% level of significance using ITT and PP population sets. Assumptions of all models and tests will be verified.

10.10 Safety Analysis

Safety and tolerability will be assessed by AEs, laboratory testing (haematology, biochemistry, and urinalysis), and vital signs.

The safety analyses will be performed using the safety population (Section 10.2). Treatment-emergent AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. Treatment Emergent Adverse events leading to death or to discontinuation from treatment and TESAEs will also be tabulated. All adverse events, regardless of whether it is treatment emergent or not, will be listed.

Laboratory data will be summarized descriptively by visit. In addition, shift tables showing the number of patients with values low, normal, and high compared to the normal ranges pre-treatment versus post-treatment will be provided for the applicable lab parameters. Change from baseline analysis will also be reported if applicable. All laboratory data will be listed.

Vital sign measurements, including weight, will be summarized descriptively by visit and presented as shift tables and listed.

10.11 Missing Data

Imputation will not be done unless stated otherwise

11. CHANGES IN THE CONDUCT OF THE TRIAL

11.1 Protocol Amendments

Any change to this Protocol will be documented in a Protocol Amendment, issued by either Algernon Pharmaceuticals or designated CRO, and agreed upon by both the Algernon Pharmaceuticals and the Investigator prior to its implementation.

Protocol amendments will be submitted for notification of Regulatory authorities and IECs in accordance with local regulations. IEC approval is required for any substantial amendment i.e. one which could affect the safety of the patients, or which entails a change to the design and/or scope of the trial.

Changes to the protocol intended to eliminate immediate hazards to trial patients may be implemented prior to IEC approval.

11.2 Deviations from the Protocol

Deviations from protocol should not occur. In the event of a deviation from protocol, the Investigator must inform the Monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented in writing (and included in e-CRF data). A set of deviations must also be accompanied by a description of the deviation, the relevant dates, and the action taken. A Log of Protocol Deviation Reports will be maintained by the Investigator or CRO. Deviation reports and supporting documentation must be kept in the Investigator's File and the Trial Master File.

11.3 Premature Trial Termination

Both the Sponsor and the Investigator (with regard to his/her participation) reserve the right to terminate the trial at any time. Should this become necessary, the procedure shall be agreed upon following consultation between Sponsor and the Investigator. Both the Investigator and the Sponsor will ensure that appropriate consideration is given to the protection of the best interests of the patients. Regulatory authorities and IECs will be informed.

In addition, the Sponsor reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include but are not limited to: insufficient adherence to protocol requirements; failure to enter patients at an acceptable rate; falsification of records; and GCP non-compliance.

12. MONITORING PROCEDURES

12.1 Study Monitoring and Source Data Verification

In accordance with applicable regulations including GCP, Monitors from the CRO will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements.

When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the e-CRF will serve as the source document.

The monitor will verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the e-CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the e-CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria, and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

Remote monitoring considerations:

Remote monitoring activities may be used as a method to assess a site's compliance with the protocol, ICH GCP and applicable regulatory requirements. Examples of when remote monitoring may be utilized are in preparation for or in between on-site monitoring visits, interim data analyses and data locks. During remote monitoring, eCRF data can be reviewed for timeliness of entry, completeness, internal consistency, protocol and ICH GCP compliance and logic. Remote monitoring activities may also include selected source data review and verification where source documents are available remotely. There are certain limitations when conducting remote monitoring as there is no physical or direct access to review source documentation, facilities and Investigational Product (IP). In exceptional circumstances, remote monitoring may be conducted in lieu of on-site monitoring, e.g. implementation of restrictive site policies due to a major COVID-19 disease outbreak or other health crises. Remote monitoring can be conducted when it is included in the study-specific monitoring plan.

12.2 Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, the Monitor may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to

implement any corrective and/or preventative actions to address any findings/issues identified. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the Sponsor immediately.

13. REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data generated and information collected during this trial will be used by the Sponsor or CRO to create a clinical trial report, which will be submitted to the Investigator for comments.

13.2 Confidentiality and Ownership of Trial Data

Any and all confidential information relating to the IP or the trial including any data and results from the trial will be the exclusive property of the Sponsor. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to the Sponsor.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

Upon conclusion of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and the Sponsor. Further details on publication are included in the Investigators' agreements.

13.3.2 Public Disclosure

In accordance with the policy of the International Committee of Medical Journal Editors (ICMJE), all clinical trials must be registered in a public clinical trials registry as a condition for publication. It is the responsibility of the Sponsor to register the trial in appropriate registries.

14. REGULATORY AND ETHICAL ASPECTS

14.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6, and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/IEC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. The Sponsor or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, and their study-related duties and functions. The Investigator should maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all patients who sign an ICF and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries, and allow direct access to patient records (e.g. medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of e-CRFs and queries.

14.3 Patient Information and Informed Consent

An English master version of the Patient Information and Informed Consent documents will be provided for translation and adaptation into local languages. If changes are made to the Patient Information and Informed Consent documents by the IEC and/or the trial sites, the amended documents must be submitted back to the Sponsor for approval.

The patient will receive a copy of the patient information and his/her signed consent.

The Investigator will obtain a freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the patient's decision to participate. The trial patient must be given ample time to consider participation in the trial, before the consent is obtained. The informed consent form must be signed and dated by the patient before he is exposed to any trial-related procedure, including screening tests for eligibility. The Investigator will also sign and date the form.

The Investigator will explain that the patients are completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for their further care and without the need to justify their decision.

If new information becomes available that may be relevant to the trial patient's willingness to continue participation in the trial, a new patient information and informed consent form will be forwarded to the

IECs (and regulatory authority, if required). The trial patients will be informed about this new information and re-consent will be obtained.

Each patient will be informed that the monitor(s), quality assurance auditor(s) assigned by sponsor or mandated by regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with ICH guideline, local laws, and local regulations.

14.4 Confidentiality

The Sponsor affirms the patient's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). The Sponsor requires the Investigator will permit the Sponsor's representatives and, when necessary, representatives from regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the patient's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the patient or his/her legal representative.

14.5 Institutional Review Board/Independent Ethics Committee

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/IEC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational product can only be supplied to an Investigator by the Sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by the Sponsor or its authorized representative. This documentation must also include a list of the members of the IRB/IEC and their occupation and qualifications. If the IRB/IEC will not disclose the names, occupations, and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/IEC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IRB/IEC and, if applicable, the authorities must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

14.6 End-of-Trial and End-of-Trial Notification

End-of-Trial is defined as the date the last patient performs the last visit in the trial. At the end of the trial, the regulatory authorities and IECs will be notified of trial completion according to national requirements.

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16. APPENDICES

16.1 National Early Warning (NEW) Score

(WHO Blueprint Master Protocol; Royal College of Physicians 2012)

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate (per minute)	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations (%)	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature (°C)	≤35.0		35.1 – 36.0	36.1 – 38.0	38.1 – 39.0	≥39.1	
Systolic BP (mmHg)	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate (per minute)	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).

The aggregate results from all 7 physiological parameters are used to obtain the NEW Score.

16.2 Extent of Dyspnea (Likert Scale)

(Pang et al, 2014)

Subject ID: _____ **Date:** _ _/_ _ _/_ _ _ _ **Clinician's Initials:** _ _ _

Time (24-hour clock): _ _h_ _

Time Period:

☐ baseline ☐ Day 2 ☐ Day 4 ☐ Day 8 ☐ Day 14/15 ☐ Day 29

☐ Not completed

How is your shortness of breath **now** compared to when you **first started this study**?

Note: for your first questionnaire (at baseline), please compare your **current** shortness of breath to your shortness of breath **when you are well**.

Grade	Shortness of Breath	Please Choose One (mark with an 'X')
+3	Markedly Better	
+2	Moderately Better	
+1	Minimally Better	
0	No Change	
-1	Minimally Worse	
-2	Moderately Worse	
-3	Markedly Worse	

DO NOT PHOTOCOPY – ONLY USE ORIGINAL FOR SUBJECT COMPLETION
Likert Dyspnea Scale Version 3.0_3Apr2020

16.3 Cough Severity Visual Analogue Scale
(Birring and Spinou, 2015)

Protocol: AGN120-3 Subject #: _____

Clinicians initials: _____Time (24-hour clock): _ _h_ _

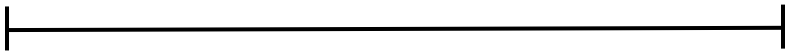
Visit #: _____ Date: _____/_____/_____
dd mmm yyyy

☐ Not completed

Cough Severity Visual Analogue Scale (VAS)

How severe has your cough been over the last 24 hours?

Rate the severity of your cough by placing a single vertical line on the scale.



No Cough Worst Cough

Date of Completion: _____(dd/mmm/yyyy)

Measurement: _____ mm (to be completed by study staff)