Protocol Title	**A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, Tolerability, Biomarkers and PK of ibudilast (MN-166) in COVID-19 Subjects at Risk for Developing Acute Respiratory Distress Syndrome (ARDS)**
Protocol Number	**MN-166-COVID-19-201**
Investigational Product	**MN-166 (ibudilast)**
Indication	**Prevention of Acute Respiratory Distress Syndrome (ARDS)**
Sponsor	**MediciNova, Inc.** **4275 Executive Square** **La Jolla, CA 92037**
Sponsor Signatory	**Kazuko Matsuda, MD PhD MPH** **Chief Medical Officer** **MediciNova, Inc.**
Date	**Original protocol dated 24 April 2020** **Amendment 1 protocol dated 18 June 2020** **Amendment 2 protocol dated 03 November 2020** **Amendment 3 protocol dated 18 February 2021** **Amendment 4 protocol dated 31 March 2021**

1.0 STATEMENT OF COMPLIANCE

This study will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (U.S.) Code of Federal Regulations (CFR), applicable country and local regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki. The Principal Investigator will assure that no changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participant.

The protocol and informed consent form will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

2.0 INVESTIGATOR AGREEMENT

PROTOCOL: MN-166-COVID-19-201 Amendment 4

I have read the foregoing protocol and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by MediciNova Inc. in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by MediciNova Inc. will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____ _____

Investigator (Print Name) Date

_____

Investigator's Signature

3.0 PROTOCOL SIGNATURE PAGE

Protocol: MN-166-COVID-19-201 Amendment 4

MediciNova, Inc.

March 31, 2021

Kazuko Matsuda, M.D., Ph.D., M.P.H.
Chief Medical Officer

Date

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5.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALI	acute lung injury
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT (SGPT)	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST (SGOT)	aspartate aminotransferase
AUC	Area under the curve
β-hCG	beta-subunit of human chorionic gonadotropin
bid	twice daily
BiPAP	Bilevel positive airway pressure
BPD	bronchopulmonary dysplasia
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
C_{max}	Maximum plasma concentration
CMP	Comprehensive Metabolic Panel
CNS	central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
CYP	cytochrome
DDI	drug-drug interaction
dL	deciliter

Abbreviation	Term
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
FDA	Food and Drug Administration
FiO_2	fraction of oxygen in inspired air
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GOLD	Global initiative for chronic obstructive lung disease
HIPAA	Health Insurance Portability and Accountability Act
HV	healthy volunteer
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
L	liter
LPS	lipopolysaccharide
MCP	monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIF	migration inhibitory factor
MMP	matrix metalloproteinase
MS	Multiple sclerosis
ms	milliseconds
NIAID	National Institute of Allergy and Infectious Diseases
PaO_2	partial pressure of oxygen in arterial blood
PCR	polymerase chain reaction
PDE	phosphodiesterase
PEEP	Positive end-expiratory pressure

Abbreviation	**Term**
PI	Principal Investigator
PK	pharmacokinetics
PT	prothrombin time
PTT	Partial thromboplastin time
qd	Once daily
RA	room air
RR	respiratory rate
RRMS	Relapsing-remitting MS
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOPs	standard operating procedures
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNFα	tumor necrosis factor alpha
TRAE	treatment-related adverse event
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

6.0 SYNOPSIS

Name of Investigational Product: MN-166 (ibudilast)
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, Tolerability, Biomarkers and PK of ibudilast (MN-166) in COVID-19 Subjects at Risk for Developing Acute Respiratory Distress Syndrome (ARDS)
Study Number: MN-166-COVID-19-201
Study Phase: Phase 2
Study Center: Multicenter
Number of Subjects (Planned): Approximately 40 patients
FPI Date: Anticipated 4Q2020
Screening Phase: up to 3 days, **Treatment Phase:** 7 days, **Follow-up Phase:** Study Day 14, 28, and Day 60
Duration of Study Drug Treatment: 7 days
Study Treatments **Test Drug:** Ibudilast (MN-166) oral 50 mg bid **Comparator Drug:** Matching placebo oral 50 mg bid **Study drug administration:** Study drug will be administrated orally. If subject becomes dependent on a gastric tube, study drug can be given via gastric tube by opening the capsules in an enteral syringe, then suspend in 30 mL distilled water. If study drug is started on Day 1 in the PM, the last dose of study drug will be taken on Day 8 in the AM.
Duration of Subject Participation: Approximately 60 days
Study Design: This is a randomized (1:1) double-blind, placebo-controlled, parallel-group study of ibudilast in hospitalized COVID-19 subjects at risk for developing ARDS receiving standard of care including anticoagulation. The study will consist of a Screening Phase followed by a Treatment and Follow-up Phase. Following the Screening Phase, if the subject meets eligibility criteria, subject will be administered treatment with MN-166 (ibudilast) or placebo. Subjects will receive ibudilast 100 mg/d (50 mg b.i.d) or placebo every day for 7 days. Upon completion of the 7-day Treatment Phase, subject will be followed-up at Day 14, Day 28 and Day 60 post baseline. **Screening Phase (up to 3 days)** The following screening assessments will be performed upon signing the ICF: inclusion/exclusion criteria review, physical examination, assess vital signs and O_2 use and SpO_2, clinical status using the NIAID scale, ECG, draw blood for plasma cytokines that include migration inhibitory factor (MIF), (interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor (TNFα), C-reactive protein (CRP) and other exploratory biomarkers. Pharmacokinetic (PK) samples, complete blood count (CBC), comprehensive metabolic panel (CMP), D-dimer, and coagulation tests will also be

drawn. A serum pregnancy test will be done in non-menopausal females. The use of prior medications taken will be recorded for 7 days prior to Day 1.

Treatment Phase (7 days)

On Day 1 (Baseline) of the Treatment Phase, hospitalized subjects will be treated with MN-166 or placebo for a 7-day period. Subjects will undergo study-related procedures including physical examination, vital signs, clinical status assessment using the NIAID scale, O_2 use and SpO_2, ECG, blood collection of biomarkers, PK (except Day 7), CBC, CMP, D-dimer and coagulation and information on adverse events and concomitant medications will be recorded. (see Table 1 Schedule of Events).

Individual patient stopping criteria based on the known safety profile of ibudilast and study stopping criteria will be implemented (see protocol sections 12.7 and 12.8).

An independent medical safety monitor will evaluate safety on an ongoing basis during the study. After each of the first three subjects are dosed, the medical safety monitor will review the data with the PI and sponsor and will make a recommendation to proceed/stop. After the first three subjects are evaluated, the medical safety monitor will continue to review safety data throughout the study.

Follow-up Phase

The Follow-up Phase consists of three visits, Day 14 (± 3 d), Day 28 (± 3 d) and Day 60 (± 7d).

Day 14

On Day 14, site staff will conduct physical examination, clinical status scale, vital signs and O_2 use, ECG, CBC, CMP, D-dimer, and coagulation tests, biomarkers, AE and conmed review, and record survival status. If subject is no longer hospitalized, a telephone follow-up to record O_2 usage and SpO_2, survival, AEs and conmeds taken will be conducted.

Day 28 (telephone follow-up if patient is no longer hospitalized)

On Day 28, the following assessments will be performed in all subjects: clinical status, O_2 therapy status use, AE and conmed review, and survival status.

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Day 60

On Day 60, the following assessments will be performed in all subjects: clinical status, O_2 therapy status, survival status, and AE and conmed review. In addition, vital signs, 12-lead ECG, and clinical safety labs (CBC, CMP, CRP, D-Dimer, PT and INR) will be performed in intubated subjects only.

Discharged prior to Study Day 7

Subjects who are discharged prior to Day 7 will be given the remainder of their study medication to be taken at home twice daily and will be given a pulse oximeter to measure their oxygen levels once daily until Study Day 14.

Primary Efficacy Objectives	***Primary Efficacy Endpoints***
To evaluate the efficacy of ibudilast vs. placebo in COVID-19 subjects measured by the proportion of subjects free of respiratory failure (i.e., decreased need for O_2 therapy)	• Proportion of subjects free from respiratory failure as defined by the need for decreased oxygen requirements (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Day 28 • Incidence of mechanical ventilation /intubation at Day 28
To evaluate the efficacy of ibudilast vs. placebo in COVID-19 subjects measured by clinical status (i.e., improvement on NIAID scale)	• Mean change from baseline in clinical status on NIAID 8-point ordinal scale at Day 28 • Percentage of patients with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale at Day 28. • All-cause mortality at Day 28
Secondary Efficacy Objectives	***Secondary Efficacy Endpoints***
To evaluate the efficacy of ibudilast vs. placebo in COVID-19 subjects measured by the proportion of subjects free of respiratory failure (i.e., decreased need for O_2 therapy)	• Proportion of subjects free from respiratory failure as defined by the need for decreased oxygen requirements (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Days 7, 14, and Day 60 • Incidence of mechanical ventilation /intubation at Day 7, Day 14, and Day 60 • Incidence of ICU admission
To evaluate the efficacy of ibudilast vs. placebo in COVID-19 subjects measured by clinical status (i.e., improvement on NIAID scale)	• Mean change from baseline in clinical status on NIAID 8-point ordinal scale at Day 7, Day 14, and Day 60 • Percentage of patients with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale at Day 7, Day 14, and Day 60 All-cause mortality at Day 7, Day 14, and Day 60
To evaluate the anti-inflammatory effects of ibudilast vs. placebo on cytokine levels	• Mean change from baseline in migration inhibitory factor (MIF), (interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alpha

	(TNFα), and C-reactive protein (CRP) at Day 7
Secondary Safety Objectives	***Secondary Safety Endpoints***
To evaluate the safety and tolerability of ibudilast versus placebo	• Incidence, frequency and severity of treatment-emergent adverse events at Days 7, 14, 28, and 60 • Mean change from baseline of the following parameters throughout the study at Days 7, 14, and 60 (in intubated subjects only): o ALT o AST o serum creatinine o BUN o complete blood count o total bilirubin o D-dimer
To evaluate pharmacokinetics (PK) of ibudilast	• PK plasma concentrations of ibudilast

Study Entry Criteria

Inclusion Criteria:

1. Written or verbal informed consent by subject or subject representative is obtained
2. Male or female subjects age 18 to 80 years, inclusive
3. SARS-CoV-2 infection confirmed with WHO criteria (including a positive PCR of any specimen, (e.g., blood, respiratory, stool, urine, or any other body fluid)
4. Chest imaging (radiograph, CT scan or lung ultrasound) with abnormalities consistent with COVID-19 pneumonia
5. $SpO_2 \leq 92\%$ on room air (RA), RR ≥24 breaths per min on RA, and/or requirement for supplemental oxygen
6. At least 1 risk factor which may put patient at higher risk for more severe illness from COVID-19: Age > 65, underlying serious heart disease, chronic lung disease, moderate to severe asthma, body mass index of ≥ 40 or diabetes
7. C-reactive protein >35 mg/L
8. No known allergies to the study drug or its excipients

Exclusion Criteria:

1. Suspected active bacterial, fungal, viral or other cause of respiratory failure other than COVID-19
2. Known or suspected immunosuppression with immunosuppressant medications or chemotherapeutic agents
3. Active primary lung cancer or another metastatic malignancy to the lungs
4. Moderate to severe liver failure (see section 12.4) defined by Child-Pugh score of ≥ 7 measured by:
    - Total bilirubin
    - Serum albumin
    - INR

- Ascites
- Hepatic encephalopathy

5. The following abnormal laboratory tests if any of the criteria are met:
   - Platelet Count < 75,000 /mm^3
   - White Blood Count < 2500 /mm^3
   - ALT or AST or Total Bilirubin >3 x ULN
   - Bilirubin > 3 mg/dL
   - Serum albumin less than 28 g/L
6. Subject is on dialysis
7. On home ventilator support or continuous domiciliary O_2 therapy for baseline lung disease
8. Active tuberculosis (TB) infection
9. Lactating or pregnant at Screening
10. History of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug
11. Treatment with an investigational drug or off-label medication within 5 half-lives or 30 days whichever is longer prior to study drug treatment
12. Participating in another COVID-19 clinical trial
13. Any other serious medical condition or abnormality that, in the Investigator's opinion, would preclude participation in the study.

Analysis Populations

Full Analysis Set: All subjects who sign informed consent, are randomized, receive treatment and have at least one post dose efficacy assessment.

Per Protocol Analysis: all randomized subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be outlined in the statistical analysis plan.

Statistical Methods

Full details of the statistical methods including handling of missing data and deaths will be outlined in the statistical analysis plan. Since this is an early proof of concept study, no formal sample size calculations have been performed.

7.0 SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Phase	Screening	Double-Blind Treatment Phase [e,g]							Follow-up		
Study Day	Day -3	Day 1 BL	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14[e] (± 3)	Day 28 (+/-3)	Day 60 (+/- 7d)
Informed consent	X										
Inclusion/exclusion criteria review	X										
Brief physical exam	X	X		X		X		X	X		
Clinical status using NIAID scale	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, RR, HR, Temp)	X	X	X	X	X	X	X	X	X		X[i]
O_2 therapy status and SpO_2	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X[a]		X[a]		X[a]		X[a]			X[i]
Biomarker plasma samples: MIF, IL-1β, IL-6, TNF-α	X[b]	X		X		X		X	X		
PK blood sample[c]		X		X		X					
CBC, CMP, CRP, D-dimer, PT, INR	X[d]	X		X		X		X	X		X[i]
Randomize [f]	X										
Administer study drug		X [h]	X	X	X	X	X	X			
Adverse event review		X	X	X	X	X	X	X	X	X	X

Prior/Concomitant medication review	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Record survival status[j]									**X**	**X**	**X**

[a] 12-lead ECG to be done between 2-4 hours after AM dose.
[b] Biomarker blood sample collection at screening is optional if Screening and Day 1 assessments occur on the same day.
[c] Collect PK samples on Day 1 in the AM prior to study drug dosing and at 2, 4, 8, and 12 hours (Predose of PM dose); Day 3 and Day 5 prior to AM study drug dosing. PK samples to be collected for 8 subjects only.
[d] Serum β-hCG for pre-menopausal women.
[e] Telephone follow-up if subject is not in hospital. If subject is no longer hospitalized or cannot return due to COVID restrictions, a telephone follow-up to record O_2 usage/levels, AEs and conmeds may be conducted. All other assessments are optional.
[f] Subjects may be randomized during the Screening Phase after all of the screening assessments are completed and subject is considered eligible for the study or on Day 1.
[g] If subject prematurely discontinues from the study or is discharged from the hospital on Days 2, 4, or 6 collect biomarker samples in addition to other scheduled assessments. If subject prematurely discontinues from the study or is discharged on Days 1, 3, 5, or 7, conduct the study assessments scheduled on those days.
[h] The first dose of study drug may be started in the AM or the PM.
[i] Vital signs, ECG and safety labs will be done in intubated subjects only.
[J] Survival status is captured on the NIAID questionnaire.

8.0 BACKGROUND

8.1 Acute Respiratory Distress Syndrome (ARDS)

ARDS is recognized as the most severe form of acute lung injury (ALI), a form of diffuse alveolar injury, which is an acute inflammatory lung process, associated with increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The acute, intense inflammatory response of the lungs occurs as a result of direct (e.g., toxins, infection) or indirect (sepsis, trauma) insult to the alveolar capillary membrane leading to increased permeability and subsequent edema from vascular leakage resulting in the loss of aerated lung tissue (Ranieri VM et al 2012, Eworuke et al 2018). ARDS is defined by timing (within 1 week of clinical insult or onset of respiratory symptoms); radiographic changes (bilateral opacities not fully explained by effusions, consolidation, or atelectasis); origin of edema (not fully explained by cardiac failure or fluid overload); and severity based on the PaO_2/FiO_2 ratio on 5 cm of continuous positive airway pressure (CPAP). The 3 categories are mild (PaO_2/FiO_2 200-300), moderate (PaO_2/FiO_2 100-200), and severe ($PaO_2/FiO_2 \leq 100$) (Ranieri VM, et al 2012).

8.2 MN-166 (ibudilast)

MN-166 (ibudilast) is a small molecule macrophage migration inhibitory factor (MIF) and phosphodiesterase (PDE) 4,10-inhibitor drug candidate with demonstrated neuroprotective action in vitro and in vivo. MIF knockout or antibody-neutralization studies have provided neuroprotection validation in certain multiple sclerosis (MS) and other neurological animal models. MN-166 (ibudilast) has additionally shown attenuation of glial cell activation in multiple in vitro and in vivo model systems which may represent a novel pharmacotherapeutic approach in ALS treatment.

MN-166 (ibudilast) distributes well to the CNS and is a selective inhibitor of the pro-inflammatory cytokine, macrophage migration inhibitory factor (MIF (Cho et al 2010) and certain cyclic nucleotide phosphodiesterases (Gibson et al 2006) at clinically relevant plasma or CNS concentrations. MIF inhibition or knockout has been linked to attenuated disease progression in animal models of multiple sclerosis (Powell et al 2005; Kithcart et al 2010) and attenuates neuronal death and promotes recovery in mouse spinal cord injury (Nishio et al 2009). Another MIF knockout study revealed its role in neurodegeneration in an experimental stroke model (Inacio et al 2011). PDE inhibition has likewise shown some neuroprotective actions (Chen et al 2007; Nakamizo et al 2003).

MN-166 (ibudilast) has been recognized to have glial attenuating activity in vitro and in vivo. In activated glia cells in vitro, MN-166 (ibudilast) suppresses the production of proinflammatory cytokines and increases the production of anti-inflammatory cytokine and various neurotrophic factors. (Suzumura et al 1999; Kawanokuchi et al 2004; Mizuno et al 2004). MN-166 (ibudilast) also protects hippocampal neurons (Tominaga et al 1996) and oligodendrocytes against excitotoxicity (Yoshioka et al 1998, 2000) and astrocytes against apoptosis (Takuma et al 2001). In an animal model of cerebral ischemia, ibudilast reduces white matter lesions and microglial

activation (Wakita et al 2003). MN-166 (Ibudilast) was also reported to reduce glial activation and attenuate allodynia in several validated animal models of peripheral and central neuropathic pain (Ledeboer et al 2007; Ellis et al 2014).

In addition, MN-166 (ibudilast) suppresses the expression of matrix metalloproteinase-9 (MMP-9) (Lee et al 2012; Yagi et al 2010). MMP-9 potentially plays an important role in the pathogenesis of ALS and when knocked down in animal models, leads to slower progression of the disease (Kaplan et al 2014).

8.3 Clinical Pharmacology

The pharmacokinetics of MN-166 has generally been shown to be dose-proportional both within and between studies. Based on prior trials, steady state plasma C_{max} and $AUC_{0\text{-}24h}$ levels at the highest dose (50 mg bid; 100 mg/day) are anticipated to be approximately 116 ng/ml (C_{max}) and 1613 ng*hr/ml ($AUC_{0\text{-}24h}$) (study AV411-026 HV group). All of the trials except for Protocol Nos. AV411-009 and AV411-016 have included all concurrent concomitant medications with ibudilast dosing at 80 or 100 mg/day. While pharmacokinetic drug-drug interactions have not been carefully assessed (or are in progress), there are no clear pharmacologic or safety interactions noted to date. Please refer to the Investigator's Brochure (IB) for tabulated summaries and details of the findings.

8.4 Rationale for Use of Ibudilast for prevention of ARDS

The rationale for the use of MN-166for prevention of ARDS is based upon its cellular and molecular target actions and recent research in ARDS animal model (D Yang, Y Yang, Y Zhao, 2020). At the molecular level, ibudilast inhibits macrophage migration inhibitory factor (MIF) and certain cyclic nucleotide phosphodiesterases (PDEs to reduce pro-inflammatory cytokines such as IL-1-beta, IL-6, and TNF-alpha (Cho et al 2010; Gibson et al 2006).

8.5 MIF Inhibition and ARDS

Macrophage migration inhibitory factor (MIF), a pro-inflammatory cytokine that not only acts on macrophages but is also produced by these cells in response to endotoxins, exotoxins, and other cytokines such as TNFα and interferon-gamma (IFN-γ) (Bach et al 2009). The critical role of MIF in mediating inflammatory lung injury in ARDS has been discussed. The study identified enhanced MIF protein expression in alveolar capillary endothelium and infiltrating macrophages in lung tissues from ARDS patients. The possibility that MIF up-regulates its synthesis in an autocrine fashion in ARDS was tested using cultured endothelial cells stimulated with MIF and a murine model of lipopolysaccharide (LPS)-induced acute lung injury. MIF induced significant TNFα synthesis in cultured endothelial cells and the effect was blocked by neutralizing anti-MIF antibody. A similar blocking effect was observed when MIF-stimulated endothelial cells were pretreated with neutralizing anti-TNFα antibody, supporting the notion that MIF induced TNFα production via an amplifying pro-inflammatory loop (Lai et al 2003).

8.6 PDE4 Inhibition and ARDS

There are multiple studies suggest that potential PDE4 inhibitors for ARDS treatment. In the animal model of ALI, roflumilast, PDE4 inhibitor treatment reduced leak of cells ($P<0.01$), particularly of neutrophils ($P<0.001$), into the lung, decreased lung edema formation ($P<0.01$), and improved respiratory parameters. The results indicate a future potential of PDE4 inhibitors also in the therapy of ALI (Kosutova et al 2017).

The anti-inflammatory effect of two PDE4 inhibitors was investigated in a pre-term rat model of hyperoxia-induced lung injury. Pre-term rat pups were exposed to room air, hyperoxia, or hyperoxia and one of two PDE4 inhibitors: rolipram and piclamilast. The anti-inflammatory effects of prolonged PDE4 inhibitor therapy were investigated by studying survival, histopathology, fibrin deposition, alveolar vascular leakage, and differential mRNA expression (reverse transcription, or RT-PCR) of key genes involved in inflammation, alveolar enlargement, coagulation and fibrinolysis. PDE4 inhibitor therapy prolonged median survival by up to 7 days and reduced alveolar fibrin deposition, lung inflammation and vascular leakage by decreasing the influx of monocytes and macrophages and protein efflux in bronchoalveolar lavage fluid.

Analysis of mRNA expression of key genes involved in experimental bronchopulmonary dysplasia (BPD) revealed a significant PDE4 inhibitor-induced improvement of genes involved in inflammation, fibrin deposition and alveolarisation. In conclusion, phosphodiesterase-4 inhibition prolongs survival by inhibiting inflammation and reducing alveolar fibrin deposition in pre-term rat pups with neonatal hyperoxic lung injury, whereby piclamilast outperformed rolipram (de Visser et al 2008).

8.7 ARDS animal model study with Ibudilast

In this study, ibudilast was tested in a LPS-induced neonatal ARDS animal model to evaluate its anti-inflammatory effect. Ibudilast ameliorated LPS-induced pathological manifestations and pulmonary edema in lung tissue. In addition, ibudilast attenuated the secretion of inflammatory cytokines TNF-alpha, IL-1 beta, IL-6 and MCP-1 by inactivating the chemokine axis and significantly reduced LPS-induced cell apoptosis in lung tissue (Yang et al 2020).

8.8 Previous Human Experience

Ibudilast is approved in Japan and South Korea for treatment of asthma (20 mg/day) and post-stroke dizziness in cerebrovascular disorders (30 mg/day) and has been prescribed for these indications for almost 30 years. The largest accumulation of clinical safety experience with ibudilast (MN-166) is from the approval of Ketas® for asthma and post-stroke dizziness. Dosing was 20 to 30 mg/day (included uses up to 40 mg/day) and based on chronic administration. In the Ketas package insert, the most common adverse events were anorexia (0.6%), nausea (0.6%), increased liver enzymes (ALT 0.4%, AST 0.3%, and GTP 0.4%). Following regulatory approval, adverse event data continued to be collected and, to date, approximately 14,968 subjects were evaluated. Safety data was taken from the 2009 Ketas package insert and Interview Forms collected from 1989 to 1996. Seven hundred sixty- nine (769) adverse drug reactions occurred in 507 (3.39%) patients. The most common (≥5%) adverse drug reactions were: itching (8; 0.05%), rash (8; 0.05%), abdominal pain (7; 0.05%), heavy head feeling (7; 0.05%), stomach

pain (7; 0.05%), epigastric discomfort (8; 0.5%), BUN increased (7; 0.05%), heart rate/heart rhythm disorders (8; 0.05%),vertigo (10; 0.7%), serum cholesterol increased (10; 0.07%), general malaise (10; 0.07%), lack of appetite (13; 0.09%), headache (13; 0.09%), heartburn (16; 0.11%), vomiting (19; 0.13%), nausea (22; 0.15%), stomach discomfort (24; 0.16%), ALP increased (36; 0.24%), AST increased (45; 0.30%), ALT increased (53; 0.35%), sickness (54; 0.36%), gamma-GTP increased (54; 0.36%), and anorexia (71; 0.47%).

9.0 CLINICAL OVERVIEW

To date, ibudilast has been evaluated in a total of 21 ongoing and completed clinical trials; 11 clinical trials by the sponsor and 10 trials by investigator and more than 750 subjects have been exposed. Eight investigator-initiated studies are conducted or ongoing in US cross-referenced to sponsor's IND. Two trials were conducted in Australia, one study targeted medication overuse headache (Australian CTN File No. 2011/012799) and the other targeted chemotherapy-induced-peripheral neuropathy (Australian CTN File No. 2018/010601). An overview of the safety profile in each of the Phase 2 clinical trials will be reported below.

9.1 MediciNova-Sponsored Studies

Among 10 completed Phase 1 and 2 studies, more than 620 received ibudilast up 100 mg/d in single and multiple doses up to 2 years.

Ibudilast was tested at dosages of 30 or 60 mg/d up to 2 years in the Phase 2 clinical trial (MN-166-CL-001) with relapsing-remitting multiple sclerosis (RRMS) patients. A total of 297 subjects were randomized; of those, 103 subjects were randomized to placebo, 95 subjects were randomized to 30 mg/d, and 99 subjects were randomized to 60 mg/d. A total of 291 subjects received ibudilast 30 mg/d or 60 mg/d for up to 2 years in the open-label-extension phase. The most common treatment related AEs were nausea, headache, and upper respiratory tract infection. There were 20 SAEs reported during entire 2-year duration of the study. All SAEs were considered not related to ibudilast in this study.

In the Phase 2 SPRINT-MS/NN102 trial, a total of 255 progressive MS subjects were enrolled, 129 subjects received doses of ibudilast up to 100 mg/d and 126 subjects received placebo for up to 96 weeks. Safety results of study SPRINT-MS/NN102 suggests that the adverse event profile of ibudilast appears to be similar to the pattern of events seen in the MN-166-CL-001 study at daily doses up to 100 mg/day. Most of the adverse events that appear to be related to ibudilast fall under the Gastrointestinal SOC, nausea, vomiting diarrhea, abdominal pain, and dyspepsia. Other treatment-related adverse events included fatigue, hepatic enzymes increased, WBC decreased, alanine aminotransferase, headache, decreased appetite, and insomnia. Although there was a higher incidence of depression in the ibudilast group, most of the events were considered to be unrelated by the principal investigator There were 58 SAEs reported in 44 subjects across both treatment groups during the 96 weeks trial. One SAE of ataxia was considered related to ibudilast, which was a single event and resolved the next day.

In the Phase 1b/2a MN-166-ALS-1201 study, 45 subjects with ALS received ibudilast 60 mg/d for up to 52 weeks. Safety results of the MN-166-ALS-1201 study also show a similar profile to the MS studies. The most commonly reported adverse events fall under the Gastrointestinal and

Nervous System SOCs. The most commonly reported TEAEs in the ibudilast group were dysphagia, nausea, fatigue, pain, upper respiratory infection, fall, weight loss, anorexia, headache, depression, insomnia, cough, and dyspnea. Treatment-related events that were attributed to ibudilast were decreased/loss of appetite, anorexia/weight loss, nausea, and ECG changes (atrioventricular junctional rhythm), and increased QTcB to upper normal of 470 (Brooks et al 2017).

In the Phase 2 open-label study (MN-166-ALS-1202) a total of 35 subjects with ALS received 100 mg/day up to 9 months. The most commonly reported treatment-related adverse event was nausea.

These studies suggest that ibudilast at daily doses of up to 100 mg/d appear to be generally safe and well-tolerated. The most commonly reported AEs have been nausea, abdominal pain, diarrhea, and headaches. There was a slight dose-related increase in the percent of subjects with headaches and gastrointestinal AEs. The incidence of nausea suggested a dose-related increase. Ibudilast also appeared to cause transient changes in laboratory values, particularly AST, ALT and GGT which, in most cases, appeared to resolve over time.

9.2 Study Dose Justification

In a preclinical model of ARDS in mice, ibudilast 7.5 mg/kg i.p. treatment significantly reduced LPS-induced pathological changes and pulmonary edema in lung tissues. In addition, ibudilast treatment attenuated the secretion of inflammatory cytokines IL-1β beta, IL-6, TNF, and MCP-1, and significantly reduced LPS-induced cell apoptosis in lung tissues.

Based on internal data, a 7.5 mg/kg dose of ibudilast administered i.p. resulted in an AUC of approximately 862 h*ng/mL, an exposure that is achieved in healthy volunteers at doses of 30-50 mg administered twice daily.

In ALS patients receiving ibudilast 100 mg per day orally, a significant reduction in MIF was observed after treatment. This effect was maintained throughout the 36-week duration of the study.

The safety of a single dose of 100 mg has been established in healthy volunteers. In addition, long term safety of up to 96 weeks of 100 mg/day doses has been established in MS and ALS patients without any significant safety sequelae. The 100 mg/day is the dose that is shown to exert significant reductions in MIF levels, and therefore considered the targeted clinical dose.

9.3 Treatment Duration Justification

According to CDC, among the COVID-19 patients who developed severe disease, the medium time to dyspnea ranged from 5 to 8 days, the median time to acute respiratory distress syndrome (ARDS) ranged from 8 to 12 days, and the median time to ICU admission ranged from 10 to 12 days. According to the published paper discussing a total of 191 COVID-19 patients treated in Wuhan, China, (Zhou et al 2020 Lancet), the median time from illness to dyspnea was 7.0 days, median time from illness to onset of ARDS was 12 days, and median time from illness to ICU admission was 12 days in total patients. The median time from dyspnea to intubation was 10.0 days (IQR 5.0–12.5) for patients who received invasive mechanical ventilation.

The steady-state plasma ibudilast concentrations are reached within 3 days of initiating b.i.d. and we want to treat at least 5 days with steady state drug level, thus, we determined duration of treatment to be 7 days.

10.0 TRIAL OBJECTIVES

10.1 Primary Objectives

The primary objectives of the study are to evaluate the:

- Efficacy of ibudilast vs. placebo in COVID-19 subjects measured by the proportion of subjects free of respiratory failure (i.e., decreased need for O_2 therapy) at Day 28;
- Efficacy of ibudilast vs. placebo in COVID-19 subjects measured by clinical status (i.e., improvement on NIAID scale) at Day28;

10.2 Secondary Objectives

The secondary objectives of the study are to evaluate the:

- Safety and tolerability of ibudilast vs. placebo in COVID-19 subjects;
- Efficacy of ibudilast vs. placebo in COVID-19 subjects measured by the proportion of subjects free of respiratory failure (i.e., decreased need for O_2 therapy) at Days 7, 14, and 60;
- Efficacy of ibudilast vs, placebo in COVID-19 subjects by clinical response of ibudilast vs. placebo in COVID-19 subjects at Days 7, 14, and Day 60;
- Anti-inflammatory effects of ibudilast vs. placebo on cytokine levels;
- Pharmacokinetics of ibudilast vs. placebo in COVID-19 subjects.

11.0 OVERALL STUDY DESIGN

This is a randomized (1:1), double-blind, placebo-controlled, parallel-group study of ibudilast in hospitalized COVID-19 subjects at risk for developing ARDS receiving standard of care. The study will consist of a Screening Phase followed by a Treatment and Follow-up Phase. Following the Screening Phase, if the subject meets eligibility criteria, subject will be randomly assigned treatment with MN-166 (ibudilast) or placebo. Upon completion of the 7-day Treatment Phase, subject will be followed-up at Day 14, Day 28, and Day 60. Subjects will receive ibudilast 100 mg/d (50 mg b.i.d) or matching placebo (50 mg b.i.d.) every day for 7 days. (See Table 1 for study assessments).

11.1 Screening

The following screening assessments will be performed upon signing the ICF: inclusion/exclusion criteria review, physical exam, assess vital signs and O_2 use and SpO_2, clinical status using the NIAID scale, 12-lead ECG, draw blood for plasma biomarkers that include migration inhibitory factor (MIF), (interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), C-reactive protein (CRP) and other exploratory biomarkers. A complete blood count (CBC), comprehensive metabolic panel (CMP), D-dimer and coagulation tests will

also be drawn. A serum pregnancy test will be done in pre-menopausal females. Prior concomitant medications taken within the last 7 days prior to study drug administration will be recorded.

11.2 Treatment Phase

During the Treatment Phase, hospitalized subjects will be treated with MN-166 or placebo for a 7-day period. During the Treatment Phase, subjects will undergo study-related procedures including physical exam, ECG, O_2 use assessment and SpO_2, biomarkers and PK samples (except Day 7) draw, CBC, CMP, D-dimer blood collection, clinical assessment using the NIAID scale, and information on adverse events and concomitant medications will be recorded (see Table 1 Schedule of Assessments).

11.3 Follow-up

On Study Day 14, if subject is still hospitalized, the site will conduct physical examination, clinical status (NIAID scale), vital signs, O_2 use and SpO_2, CBC, CMP, D-dimer, coagulation tests, biomarkers, and AE and concomitant medications review.

On Study Day 28, subject's clinical status (NIAID scale) and survival status will be recorded, O_2 therapy status use, AE and conmed review. A telephone follow-up is permitted if subject is no longer hospitalized.

On Study Day 60, subjects will undergo the following assessments: clinical status using the NIAID scale, O_2 therapy status, survival status, AE and conmed review. In addition, vital signs, 12-lead ECG, and clinical safety labs (CBC, CMP, CRP, D-Dimer, PT and INR) will be performed in intubated subjects only.

11.4 Early Termination/Discharge from Hospital

If subject early terminates from the study or is discharged from the hospital on Days 2, 4, or 6, the site will conduct clinical assessment, take vital signs, O_2 use and SpO_2, draw biomarker sample, and review AEs and concomitant medications. If subject early terminates from the study or is discharged on Days 1, 3, 5, or 7, the site will conduct the study assessments scheduled on those days.

Subjects who are discharged prior to Day 7 will be given the remainder of their study medication to be taken at home and a pulse oximeter supplied by the sponsor to measure their O_2 levels once daily until Study Day 14.

12.0 SELECTION OF SUBJECTS

12.1 Study Population

This study will enroll approximately 40 subjects diagnosed with COVID-19 who are at risk for developing acute respiratory distress syndrome (ARDS) receiving standard of care including anticoagulation. Randomization of subjects will be stratified by use of IL-6 antibody therapy.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria are not eligible to participate in the study.

12.2 Inclusion Criteria

1. Written or verbal informed consent by subject or subject representative is obtained
2. Male or female subjects age 18 to 80 years, inclusive
3. SARS-CoV-2 infection confirmed with WHO criteria (including a positive PCR of any specimen, e.g., blood, respiratory, stool, urine, or any other body fluid)
4. Chest imaging (radiograph, CT scan or lung ultrasound) with abnormalities consistent with COVID-19 pneumonia
5. $SpO_2 \leq 92\%$ on room air (RA), RR ≥24 breaths per min on RA, and/or requirement for supplemental oxygen
6. At least 1 risk factor which may put patient at higher risk for more severe illness from COVID-19: Age > 65, underlying serious heart disease, chronic lung disease, moderate to severe asthma, body mass index of ≥ 40 or diabetes
7. C-reactive protein >35 mg/L
8. No known allergies to the study drug or its excipients

12.3 Exclusion Criteria

1. Suspected active bacterial, fungal, viral, or other cause of respiratory failure other than COVID-19
2. Known or suspected immunosuppression with immunosuppressant medications or chemotherapeutic agents
3. Active primary lung cancer or another metastatic malignancy to the lungs
4. Moderate to severe liver failure (see section 12.4) defined by Child-Pugh score of ≥ 7 measured by:
    - Total bilirubin
    - Serum albumin
    - INR
    - Ascites
    - Hepatic encephalopathy
5. The following abnormal laboratory tests if any of the criteria are met:
    a. Platelet Count < 75,000 /mm3
    b. White Blood Count < 2500 /mm3
    c. ALT or AST or Total Bilirubin >3 x ULN
    d. Bilirubin > 3 mg/dL
    e. Serum albumin less than 28 g/L
6. Subject is on dialysis
7. On home ventilator support or continuous domiciliary O_2 therapy for baseline lung disease
8. Active tuberculosis (TB) infection
9. Lactating or pregnant at Screening

10. History of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug
11. Treatment with an investigational drug or off-label medication within 5 half-lives or 30 days whichever is longer prior to study drug treatment
12. Participating in another COVID-19 clinical trial
13. Any other serious medical condition or abnormality that, in the Investigator's opinion, would preclude participation in the study.

12.4 Child-Pugh Scoring Table

Subjects will be excluded from study if Child-Pugh score at screening is ≥7.

Table 2 Child-Pugh Scoring Table

Measure	1 point	2 points	3 points
Bilirubin (total) mg/dL	<2	2-3	>3
Serum albumin g/L	>35	28-35	<28
INR	<1.7	1.71-2.20	>2.20
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

12.5 Screen Failures

A Screen failure is defined as a potential subject who did not meet one or more criteria required for participation who consent to participate in the clinical trial but is not subsequently randomly assigned to the study intervention or entered in the study.

Individuals who do not meet the criteria for participation in this trial (screen failure) due to abnormal clinical laboratory results may be rescreened. Study staff should notify sponsor prior to rescreening.

12.6 Subject Withdrawal/Discontinuation Criteria

A subject may request to be withdrawn from the study at any time for any reason.

The Investigator may interrupt the treatment of any subject whose health or well-being may be compromised by continuing participation in the study. The following instances require subjects to be withdrawn from the study:

- Subject fails to adequately comply with the dosing, evaluations, or other requirements of the study at the discretion of Investigator
- Subjects who have adverse events that require discontinuation of study medication
- Subjects who, in the opinion of the Investigator, should be discontinued for their well-being

- Subjects who are no longer able to understand task instructions or to perform tests adequately
- Subject becomes pregnant during the study. See Section 18 for reporting requirements and follow-up of the pregnancy

If a subject withdraws or is removed from the study for any reason, the reason and date of discontinuation of study medication should be recorded in the appropriate section of the Case Report Form (CRF). At the time of study discontinuation, every effort should be made to ensure that the scheduled study procedures and evaluations for that day are performed. Subjects who are discontinued from study drug for reasons other than loss to follow-up or withdrawal of consent will remain in the study and continue regularly scheduled efficacy and safety assessments.

The study sponsor reserves the right to discontinue the study at any time for medical or administrative reasons.

12.7 Subject Stopping Criteria

A subject should be withdrawn from the study if any of the following abnormal lab values occur, **after repeat testing:**

- AST or ALT or total bilirubin >3 x upper limit of normal (ULN)
- Bilirubin >3 mg/dL
- Serum albumin less than 28 g/L
- White blood count <2500/mm^3
- Platelet count <75,000/ mm^3

A subject should also be withdrawn from the study if any of the following adverse events occur:

- Nausea considered moderate or severe and related to study drug by investigator for greater than 3 consecutive days despite maximal supportive therapy
- Vomiting considered moderate or severe and related to study drug by investigator for greater than 3 consecutive days despite maximal supportive therapy
- Diarrhea considered moderate or severe and related to study drug by investigator for greater than 3 consecutive days despite maximal supportive therapy
- Occurrence of an SAE or grade 3 adverse event related to study drug

Subjects who are withdrawn/discontinued from study drug to an abnormal lab result or adverse event will remain in the study and continue regularly scheduled efficacy and safety assessments.

12.8 Study Stopping Criteria

An independent medical safety monitor will evaluate safety on an ongoing basis during the study. After each of the first three subjects are dosed, the medical safety monitor will review the data with the PI and sponsor and will make a recommendation to proceed/stop. After the first three subjects are evaluated, the medical safety monitor will continue to review safety data throughout the study.

If two or more subjects experience similar adverse events of moderate or severe intensity or similar serious adverse events related to study drug or if two or more subjects discontinue study treatment due to safety concerns, study dosing will be temporarily halted until the safety data has been reviewed. Once reviewed by an independent safety monitor, sponsor and PI, a determination will be made to continue or stop the study.

13.0 TREATMENTS

MN-166 (ibudilast) will be administered as MN-166 50 mg (5 capsules) b.i.d for 7 days. Study drug may be taken with food or within an hour of eating to improve gastrointestinal tolerability. Subjects who cannot tolerate a b.i.d. dosing regimen may be administered a t.i.d. dosing regimen (40 mg at breakfast, 30 mg at lunch, 30 mg dinner). Subjects who cannot tolerate this regimen will be discontinued from the study.

Day 1 study drug may be administered starting with the PM dose. If the first dose of study drug is administered in the PM then the last dose should be administered on Study Day 8 in the AM.

Matching placebo will also be provided and will be administered as 50 mg (5 capsules) b.i.d. for 7 days.

13.1 Study Drug Supply

MN-166 and matching placebo will be provided in 10 mg non-vegetarian capsules in polyethylene bottles and will be stored at room temperature.

MN-166 is an extended release pharmaceutical preparation comprised of white extended release granules contained in a No.4 white capsule (Table 3).

Table 3 Study Drug Information

Investigational Drug	MN-166 or matching placebo
Formulation	10 mg capsules
Frequency	MN-166: 50 mg b.i.d. for 7 days
Storage Conditions	Store at room temperature

13.2 Study Drug Packaging and Labeling

At a minimum, the following information will be included on each package:

- Name of Sponsor
- Study number/Acronym/IND number
- Route of administration
- Quantity of dosage unit
- Directions for use
- Storage conditions
- Space for information to be completed by Investigator/designee:
  - Name and telephone number of Investigator

  - Dispensing date
  - Subject number
- Statement "Caution: New Drug – Limited by federal law to investigational use"

13.3 Study Drug Storage

The study drug should be stored at room temperature. Do not freeze.

13.4 Study Drug Administration

The study drug will be dispensed by appropriately qualified site study staff.

Investigational clinical supplies will be received by the PI or a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and/or designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol.

Study drug will be administrated orally. If subjects become dependent on a gastric tube, study drug can be given via gastric tube by opening the capsules in an enteral syringe, then suspend in 30 ml distilled water. It is recommended that the gastric tube is rinsed before and after each study drug delivery via gastric tube. Study drug is extended-release granule in gelatin capsule and gelatin capsule has no functionality in the release of drug.

Also, open capsule MN-166 administration has been used in 2 clinical trials in ALS patients who became gastric tube dependent due to bulbar symptoms, with no safety concerns.

13.5 Dose Interruptions

The following abnormal laboratory tests should be repeated within 24 hours if any of the criteria are met:

- AST or ALT or Total Bilirubin >3 x upper limit of normal (ULN)
- Bilirubin >3 mg/dL
- Serum albumin less than 28 g/L
- White blood count <2500/mm3
- Platelet count <75,000/ mm3

If, after repeat testing, the laboratory value is still outside the above-stated limits, then the subject should stop study medication. While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in the protocol (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice).

13.6 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a randomization scheme generated by a computer program. The randomization scheme will be reviewed and approved by an independent statistician from the Sponsor and locked after approval.

13.7 Blinding

The subject and all study staff members including the Sponsor will be blinded to the treatment codes. Randomization information will be kept strictly confidential, filed securely by an appropriate group at the sponsor company and accessible only to authorized personnel until the time of unblinding.

13.8 Prohibited Medication

The use of any unauthorized investigational therapy is prohibited during the study.

13.9 Treatment Compliance

Records of treatment compliance for each subject will be kept throughout the study. The clinical research monitor will review treatment compliance during site visits and at the completion of the study.

14.0 STUDY PROCEDURES

14.1 Informed Consent

The Principal Investigator or a qualified designee (e.g., a licensed, qualified medical practitioner such as a physician's assistant or a nurse practitioner) listed on FDA Form 1572 will explain the study to the subject or subject's representative, answer all of the subject's questions, and obtain written or verbal informed consent before performing any study-related procedure. Informed Consent should be conducted in accordance with local requirements. Subject should be able to verbally describe the benefits and risks associated with this study and what other treatment alternatives are available (as described in the Informed Consent form).

Only subject or subject's representative who provide informed consent, as assessed and documented by the Investigator, will be enrolled. The subject is required to provide written informed consent prior to undergoing any study procedures. If subject is unable to sign their full name, an "X" can be acceptable. A copy of the signed and dated informed consent (in a language in which the subject is fluent) is required to be given to the subject. If a subject withdraws consent, data collected up to the time of discontinuation will be used to evaluate study results.

14.2 Clinical Lab Testing

Clinical laboratory testing (CMP, CBC, and coagulation) will be performed at Screening, Day 1, Day 3, Day 5, Day 7, Day 14 and Day 60 (in intubated subjects only) at the site's local laboratory.

Table 4 CMP, CBC, and Coagulation Tests

Comprehensive Metabolic Panel (CMP)	Complete Blood Count (CBC) with Diff
Serum albumin	white blood cell count (WBC)
blood urea nitrogen (BUN)	white blood cell differential
calcium	eosinophilic leukocyte count
carbon dioxide (bicarbonate)	basophilic leukocyte count

chloride	neutrophil count
Serum creatinine	lymphocyte count
glucose	monocyte count
potassium	platelet count
sodium	red blood cell count (RBC)
total bilirubin	hemoglobin
total protein	hematocrit
alanine aminotransferase (ALT)	D-dimer
alkaline phosphatase (ALP)	PT
aspartate aminotransferase (AST)	INR
GFR (estimated- will be autocalc by database)	

14.3 Biomarker Samples

The biomarker samples, migration inhibitory factor (MIF), (interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor (TNFα), C-reactive protein (CRP), and other exploratory markers will be sent to a central laboratory. Biomarker samples will be collected at Screening, Day 1, Day 3, Day 5, Day 7, and Day 14. See Laboratory Manual for biomarker sample collection, processing, and shipping.

14.4 Pharmacokinetic (PK) Samples

Pharmacokinetic samples will be collected on Day 1: AM Predose, and at 2, 4, 8 and 12 hours (Predose of PM dose), and on Day 3 and Day 5 at AM Predose.

PK samples will be collected for 8 subjects only.

See Laboratory Manual for PK collection, processing, and shipping.

14.5 Clinical Assessment Scale

At Screening and on Study Days 1 through 7, and on Days 14 28, and Day 60 of the Follow-up visits, subjects will be assessed using the NIAID 8-point ordinal scale:

1) Death;

2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;

4) Hospitalized, requiring supplemental oxygen;

5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;

7) Not hospitalized, limitation on activities and/or requiring home oxygen;

8) Not hospitalized, no limitations on activities

15.0 STUDY ASSESSMENTS

15.1 Screening

After signing of informed consent form the following assessments will be performed:

- Inclusion/Exclusion criteria review
- Conduct brief physical exam
- Assess clinical status using NIAID scale
- Assess vital signs (BP, RR, HR, Temp)
- Conduct ECG
- Assess O_2 use including CPAP, BiPAP, and nasal cannula and SpO_2
- Collect blood sample for biomarkers *(MIF, IL-1β, IL-6, TNF-α)
- Complete blood count (CBC), comprehensive metabolic panel (CMP), CRP, D-dimer, and coagulation test (PT and INR)
- Collect serum β-hCG in pre-menopausal women
- Record prior medication use within the past 7 days prior to study drug administration

*Biomarker blood sample collection is optional at Screening if the Screening and Day 1 assessments occur on the same day but the sample must be collected pre-study drug dosing.

15.2 Randomization

Once all of the screening assessments have been conducted, subject will be randomized. Randomization will be stratified according to subject's use of IL-6 antibody therapy and may occur on either the last day of screening or the morning of Day 1.

15.3Treatment Phase

15.3.1 Day 1 (Baseline), Day 3, Day 5 and Day 7

- Brief physical exam
- Assess clinical status using NIAID scale
- Assess vital signs (BP, RR, HR, Temp),
- Assess O_2 use including invasive mechanical ventilation, non-invasive ventilation (CPAP, BiPAP, nasal cannula high-flow oxygen), or ECMO and SpO_2
- 12-lead ECG (check between 2-4 hours after AM dose of study drug)
- Collect blood sample for biomarkers (MIF, IL-1β, IL-6, TNFα)
- Collect PK samples (except Day 7)
- Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), CRP, D-dimer, PT, INR
- Adverse events review
- Concomitant medication review

- Administer study drug (Study drug is administered every day on Days 1 through 7)

15.3.2 Day 2, Day 4, and Day 6

- Assess clinical status using the NIAID scale
- Assess vital signs (BP, RR, HR, Temp)
- Assess O_2 use including invasive mechanical ventilation, non-invasive ventilation (CPAP, BiPAP, nasal cannula high-flow oxygen), or ECMO and SpO_2
- Administer study drug
- Adverse events review
- Concomitant medication review

15.3.3 Follow-up Phase (Day 14 Day 28 and Day 60)

The Follow-up Phase consists of a Day 14, Day 28, and Day 60 visit.

Day 14

- Brief physical exam
- Assess clinical status using NIAID scale
- Assess vital signs (BP, RR, HR, Temp)
- Assess O_2 use including invasive mechanical ventilation, non-invasive ventilation (CPAP, BiPAP, nasal cannula high-flow oxygen), or ECMO and SpO_2
- Collect blood sample for biomarkers (MIF, IL-1β, IL-6, TNFα)
- Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), CRP, D-dimer, PT, INR
- Adverse events review
- Concomitant medication review

If subject is no longer hospitalized or cannot return due to COVID restrictions,
a telephone follow-up to record O_2 usage/levels, AEs and conmeds may be conducted. All other assessments are optional.

Day 28

- Assess clinical status using NIAID scale
- Assess O_2 use including invasive mechanical ventilation, non-invasive ventilation (CPAP, BiPAP, nasal cannula high-flow oxygen), or ECMO and SpO_2
- Survival status
- Adverse events review
- Concomitant medication review

If subject is not in the hospital, a telephone follow-up may be conducted.

Day 60

The following assessments will be performed in all subjects:

- Assess clinical status using NIAID scale
- Assess O_2 use including invasive mechanical ventilation, non-invasive ventilation (CPAP, BiPAP, nasal cannula high-flow oxygen), or ECMO and SpO_2
- Survival status
- Adverse events review
- Concomitant medication review

In addition, for subjects who are intubated (at screening or during the study) perform the following:

- Vital signs (BP, RR, HR, Temp)
- 12-lead ECG
- Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), CRP, D-dimer, PT, INR

15.3.4 Early Termination/Discharged from Hospital

If subject is no longer hospitalized or cannot return due to COVID restrictions, a telephone follow-up to record O_2 usage, AEs and conmeds taken will be conducted. All other assessments are optional.

If subject terminates early from the study or is discharged from the hospital prior to completion of the Treatment Phase, complete assessments scheduled for that Study Day. If subject discontinues or are discharged on Days 2, 4, or 6, collect a biomarker sample in addition to their regularly scheduled assessments.

Subjects who are discharged prior to Day 7, will be given their study medication to be taken at home and a pulse oximeter (ClinicalGuard CMS-50DL Fingertip Pulse Oximeter) supplied by the sponsor to record their O_2 saturation once daily until Day 14.

16.0 SAFETY ASSESSMENTS

Adverse events (serious and non-serious) including all Suspected Unexpected Serious Adverse Reactions (SUSARs) should be collected from time of first dose of study drug until the end of their participation in the study (i.e., the subject has discontinued or completed the follow-up visit).

The PI or a qualified designee listed on Form FDA 1572 must assess the severity and relationship to study medication for all AEs.

The PI, sub-investigator (Sub-I) and members of the clinical research team are responsible for identifying adverse events and reporting them to the RN/study coordinator.

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality and indicate that assessment on the CRF. For treatment-emergent AEs with a causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Sponsor concurs with that assessment.

16.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a study subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational medicinal product, whether or not considered related to the investigational medicinal product. Adverse events may include the onset of a new illness and the exacerbation of pre-existing conditions.

16.2 Assessment of Adverse Events

The PI or will assess all AEs for severity, relationship with study medication, and whether it meets the criteria for classification as a SAE, requiring immediate notification to the Sponsor or designee. These assessments will be made in accordance with the standard ratings detailed in the following sections.

16.3 Severity Assessment

The severity of AEs will be determined as described in Table 5.

Table 5 Adverse Events Severity Definitions

Mild Grade 1	Ordinarily transient symptoms that do not influence performance of subject's daily activities.
Moderate Grade 2	Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities.
Severe Grade 3	Symptoms cause considerable discomfort. Substantial influence on subject's daily activities.
Life-threatening Grade 4	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization probable.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

16.4 Relationship to Study Drug

One of the following categories in Table 6 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 6 Adverse Events Causality Definitions

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which cannot be explained by concurrent disease or other medications or chemicals.
Probably related	A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other medications or chemicals, and which follows a clinically reasonable response on withdrawal.
Possibly related	A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other medications or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely related	A clinical event, including laboratory test abnormality, occurs with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other medications, chemicals, or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, occurs with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other medications or chemicals).

16.5 Recording Adverse Events

Adverse events should be collected and recorded for each subject from the date the patient receives study drug until the end of their participation in the study, (i.e., the subject has discontinued or completed the study) through the follow-up visit.

Adverse events may be volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as, “How have you been feeling since you were last asked?” All AEs and any required remedial action will be recorded in the subject’s source documentation and transcribed onto the appropriate CRF page for the study period indicated. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be documented together with the PI’s or an authorized physician’s assessment of the

seriousness of the AE and causal relationship to study medication and/or study procedure (at the time of assessment).

All AEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the PI or an authorized physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the most current version of MedDRA.

16.6 Treatment and Follow-Up of Adverse events (AEs)

Appropriate measures should be taken to treat AEs as necessary, and the response of the study subject should be monitored and recorded. Clinical, laboratory, and diagnostic measures should be obtained as needed, and the results of which should be recorded in the subject's source documentation and transcribed onto the appropriate CRF page.

All SAEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

16.7 Serious Adverse Events (SAEs)

An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening (i.e., a subject is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is another important medical event (see below)

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse. A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity, but would probably not be considered an SAE.

16.8 SAE Reporting Requirements

The PI or an authorized delegate is responsible for faxing the requested SAE information to the Sponsor or designee within 24 hours or as soon as possible after learning of the event. Following

the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Notification of the SAE must be sent by fax (+01 858-404-0048) or email (safetyreports@medicinova.com) in the form of a completed SAE Report to the Sponsor. As a minimum requirement, the initial notification should provide the following information:

- Study number
- Subject number
- Gender
- Date of birth
- PI's name and full study site address
- Details of SAE
- Criterion/criteria for classification as "serious"
- Study medication name, or code if blinded, and treatment start date
- Date of SAE onset
- Causality assessment

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports, etc.), with the study subject's personal identifiers removed. All relevant information obtained by the PI or an authorized delegate through review of these documents will be recorded on the AE eCRF page and/or a new SAE Report Form and faxed to the Sponsor or designee within 24 hours of receipt of the information. If a new SAE Report Form is faxed, the PI must sign and date the form. The Sponsor may also request additional information on the SAE, which the PI or an authorized delegate must fax to the Sponsor (+01 858-404-0048) or designee within 24 hours of the request using a new SAE Report Form, bearing the PI's signature and date.

Any AE fulfilling the criteria for expedited reporting will be reported by the Sponsor to regulatory authorities and Investigators and IRB/IEC(s) in accordance with the Sponsor's standard operating procedures (SOP) and local regulatory requirements.

The PI should report all Investigational New Drug Application safety alerts received from the Sponsor to the local or central IRB.

17.0 GUIDANCE FOR OVERDOSE

There is no clinical experience with MN-166 overdose in humans and there is no available specific antidote (i.e., rescue protocol) to the effects of MN-166. Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose.

18.0 REPORTING AND FOLLOW-UP OF PREGNANCIES

If any study subject or subject's partner becomes pregnant after receiving the first dose of study medication and until the follow-up period specified in the protocol, the PI or an authorized delegate should submit a Pregnancy Report Form to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the pregnancy. If a pregnancy is to be terminated,

the anticipated date of termination should also be provided in the "Additional Information/Comments" field of the Pregnancy Report Form. If a maternal SAE is reported for the study subject during the initial notification of pregnancy, a separate SAE Report Form should also be completed and submitted to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the SAE.

Subjects who become pregnant while in the study should be followed for the duration of their pregnancy. If the pregnancy is discovered between regularly scheduled study visits, subjects should return for an unscheduled visit to return their study medication. A quantitative β-hCG should be obtained and subjects should be encouraged to return for follow-up visits. If follow-up visits are not possible, the PI should collect information about the pregnancy such as spontaneous or elective termination, details of birth, and presence or absence of birth defects, congenital abnormalities, or maternal and newborn complications.

The Sponsor will request that the PI follow the progress of the study subject's pregnancy with the doctor medically responsible for the pregnancy. A new Pregnancy Report Form should be submitted within 24 hours of the PI or an authorized delegate first becoming aware of any new information.

If additional information on the outcome of the pregnancy and/or the details of the birth/delivery is received "spontaneously" by the study site, the PI or authorized delegate should also submit a Pregnancy Report Form within 24 hours of becoming aware of the information. If the outcome of the pregnancy is reported as premature birth, or as elective termination due to a medical reason or as spontaneous or accidental miscarriage, the details of the outcome should be described in the "Additional Information/Comments" field of the Pregnancy Report Form. The pregnancy outcome will generally be reported as a follow-up report.

An SAE Report Form should be completed if the delivery outcome meets the criteria for a SAE (e.g., congenital anomaly/birth defect, stillbirth, some other sickness, etc.). The SAE Report Form should be completed with the study subject's details (e.g., subject number, initials, date of birth, investigational product information, etc.) and the details of the fetal SAE and maternal complications should be described in the "Narrative" field of the SAE Report Form.

If a pregnancy is reported for the study subject's partner, the sponsor will provide instructions on how to collect pregnancy information in accordance with local requirements.

19.0 STATISTICAL CONSIDERATIONS

Full details of the statistical methods including handling of missing data and deaths will be outlined in the statistical analysis plan. Since this is an early proof of concept study, no formal sample size calculations have been performed.

19.1 Analysis Population

Full Analysis Set: All subjects who sign informed consent, are randomized, receive treatment and have at least one post dose efficacy assessment.

Per Protocol Analysis: all randomized subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be outlined in the statistical analysis plan.

19.2 Primary Endpoints

- Proportion of subjects free from respiratory failure as defined by the need for decreased oxygen requirements (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Day 28
- Incidence of mechanical ventilation /intubation at Day 28
- Mean change from baseline in clinical status using the NIAID 8-point ordinal scale at Day 28
- Percentage of patients with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale at Day 28
- All cause mortality at Day 28

19.3 Secondary Endpoints

- Incidence, frequency, and severity of adverse events at Day 7, 14, 28, and Day 60 Mean change from baseline of the following parameters at Day 7, 14, and Day 60 (in intubated subjects only):
    - Mean change from baseline in ALT
    - Mean change from baseline in AST
    - Mean change from baseline in serum creatinine
    - Mean change from baseline in BUN
    - Mean change from baseline in complete blood count
    - Mean change from baseline total bilirubin
    - Mean change from baseline in D-dimer
- Proportion of subjects free from respiratory failure as defined by the need for decreased oxygen requirement (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Days 7, 14, and Day 60
- Incidence of mechanical ventilation /intubation at Day 7, Day 14, and Day 60
- Incidence of ICU admission
- Mean change from baseline in clinical status using the NIAID 8-point ordinal scale at Days 7, 14, and Day 60
- Percentage of patients with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale at Day 7, Day 14, and Day 60
- All-cause mortality at Days 7, 14, and Day 60
- Mean change from baseline in migration inhibitory factor (MIF), interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor (TNFα), and C-reactive protein (CRP) at Day 7
- PK plasma concentrations

19.4 Safety Analysis

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of study medication), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be

summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness.

19.5 Pharmacokinetic Analysis

Plasma concentrations of MN-166 will be summarized.

20.0 ETHICS

20.1 Ethics Review

Documented approval from the IRB will be obtained for all participating centers prior to clinical trial start, according to ICH (International Conference on Harmonization) GCP, local laws, regulations, and organization. When necessary, an extension, amendment or renewal of the IRB approval must be obtained.

20.2 Ethical Conduct of the Study

The procedures set out in this clinical trial protocol pertaining to the conduct, evaluation, and documentation of this clinical trial, are designed to ensure that the Sponsor and Principal Investigator abide by Good Clinical Practice Guidelines (GCP). The clinical trial will also be carried out in accordance with applicable local law(s) and regulation(s).

20.3 Written Informed Consent

An information and consent form will be provided to the subject. The process of obtaining informed consent must be in accordance with applicable regulatory requirements and must adhere to GCP and ethical principles in the Declaration of Helsinki. Written informed consent must be obtained and documented before any clinical trial-specific procedure takes place. Participation in the clinical trial and date of informed consent given by the subject must be documented in the subject files.

20.4 Confidentiality

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees.

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"Model" Informed Consent

This is a "Model" informed consent provided by MediciNova, Inc., only as a guide for the convenience of the Principal Investigator and the affiliated institution. It is the responsibility of each Investigator and institution to draft and obtain IRB/EC/REB approval of an Informed Consent that complies with Regulatory guidelines and ethical standards for their particular site. Any use, in whole or in part, of this "Model" Informed Consent shall be at the sole discretion of said Investigator and institution, and MediciNova, Inc., shall have no liability for the form or content of the Informed Consent adopted for actual use by said Investigator and institution.

Subject Information Sheet and Consent Form

Protocol Number	**MN-166-COVID-19-201**
Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety, Tolerability, Biomarkers and PK of ibudilast (MN-166) in COVID-19 Subjects at Risk for Developing Acute Respiratory Distress Syndrome (ARDS)
Principal Investigator (Study Doctor)	
Sponsor	**MediciNova, Inc.** 4275 Executive Square Suite 300 La Jolla, CA 92037
Sponsor Contact	**Kazuko Matsuda, MD, PhD, MPH** Chief Medical Officer, MediciNova, Inc. (858) 373-1500
Date	**31 March 2021**

Invitation to Participate in a Research Study

You are being asked to participate in a research study because you are at risk for developing Acute Respiratory Distress Syndrome, or ARDS. In order to decide whether or not to take part in this research study, you should know enough about its risks and benefits to make a decision. This process is called informed consent.

The following information is provided in order to help you make an informed decision whether or not to participate in this study. Please read this consent form carefully and take your time making your decision. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You will receive a copy of this signed and dated consent form to keep. For the purposes of this research, you will be referred to as a "**participant**."

It is expected that about 40 people will take part in this research study.

MediciNova, Inc, a pharmaceutical company, is the sponsor of the study and is providing funding for the research study, including the study drug.

XXX Hospital will be paid by the sponsor to conduct this research study.

Purpose of this Research Study

You are being asked to take part in this Phase 2 research study to evaluate the safety and tolerability of ibudilast (also called MN-166) compared to placebo (pills that looks like MN-166 capsules but contain no active medicine). Ibudilast is the investigational drug (study medication) being studied. 'Investigational' means that the drug has not been approved for treatment of any indication by the U.S. Food and Drug Administration (FDA).

This is the first study to test ibudilast in subjects who have been diagnosed with COVID-19 and are at risk for developing ARDS.

The study will be conducted at two study sites and approximately 40 subjects will be involved in this research study which will last for approximately 30 days in non-intubated patients and 60 days in patients who are intubated days.

The purpose of this study is to see if ibudilast can help prevent acute respiratory distress syndrome (ARDS), a serious lung injury in patients who are diagnosed with COVID-19 and have an increased risk of developing ARDS such as:

- **Age greater than 65 years old**
- **Serious heart disease**
- **Chronic lung disease**
- **Moderate to severe asthma**
- **Diabetes, and/or**

- **Have a BMI (body mass index) at or greater than 40.**

Ibudilast has been approved in Japan for over 30 years for treatment of post-stroke dizziness and asthma. However, ibudilast has not been approved by the US Food and Drug Administration (FDA) for use in the US, Canada and Europe. This means that ibudilast can only be used in research studies. So far, this drug has been given to more than 750 people who have participated in clinical trials including healthy volunteers, people with diabetes who have nerve pain, and people with multiple sclerosis and amyotrophic lateral sclerosis (ALS).

What should you know before you give consent?

You are at risk for developing ARDS (acute respiratory distress syndrome) and are now considering the use of ibudilast because your doctor believes that ibudilast may help prevent it from occurring.

Before you consent to receiving treatment with ibudilast, you must be informed of the following:

- In this study, you will receive standard of care and will have all the standard medications and procedures given for your condition.
- Ibudilast is not proven to prevent ARDS, therefore, there is no promise that your condition will not get worse;
- You do not have to take this experimental drug and your decision about what to do must be made voluntarily.

The experimental drug, Ibudilast, has not received approval for use in humans from the U.S. Food and Drug Administration (FDA). Research studies to see how safe and how effective this drug treats diseases have been conducted and future clinical trials are possible. Your study doctor has agreed to be the *Principal Investigator*, that is, they accept the responsibilities that come along with treating a patient with an experimental drug. These responsibilities include, but are not limited to, the following:

- Carrying out the research study as described;
- Monitoring you for safety, tolerability, and changes in your condition, if any, throughout the course of treatment and post-treatment;
- Submitting the necessary documents to the FDA, Institutional Review Board (IRB), and the sponsor throughout the course of treatment and follow-up.

What will happen to you during the study?

In order to enroll in the study, you will have to review and sign this Information and Informed Consent Form before having any study-specific procedures to determine if you are eligible to participate.

The study consists of a Screening Phase, a 7-day double-blind Treatment Phase and a Follow up Phase consisting of Day 14, Day 28 and Day 30 visits. Screening procedures may be done over a 3-day period. Study drug will be given to you twice a day (at around breakfast and dinner time) for 7 days. Two days after you finish taking study drug, you will be assessed for clinical status and side effects. At 30 days after taking study drug, you will have a follow-up call to see how you are doing.

If you are eligible to participate, you will be randomized to one of two study drug treatments. "Study drug" used in this consent form refers to both MN-166 and placebo. Being randomized means that you are put in a group by a chance process, like flipping a coin. You won't know what group you are in and neither will your study doctor, study team or sponsor. You will have a 1 out of 2 (or 50%) chance of being assigned to the MN-166 group and 1 out of 2 (or 50%) chance of being assigned to the placebo group. The placebo looks like ibudilast but does not contain the active drug. Although you and your doctor will not know which study drug you are receiving, this information can be determined in the event of an emergency.

During the study, and after signing the Information and Consent form, the following procedures and assessments will be done.

Screening Procedures:

- Confirm that you are eligible to participate in the study
- A physical exam will be done
- Your clinical status will be assessed using a brief questionnaire
- Your vital signs (blood pressure, heart rate, pulse, and temperature) will be taken
- A 12-lead ECG will be performed
- Your oxygen use including CPAP, BiPAP, and nasal cannula will be assessed
- A blood sample to collect biomarkers and routine clinical labs (complete blood count and comprehensive metabolic panel) will be taken from a needle in your arm for routine laboratory tests and biomarkers (to measure inflammation in your body). The total amount of blood that will be taken will be about 2 tablespoons;
- If you are a female of child-bearing potential, you will be given a pregnancy test;
- You will be asked to report any prior medications taken within 7 days of starting the investigational drug;

Upon review of all labs, tests and clinical status, **Dr. XXX** or a designated study associate, will speak with you about beginning participation in this research study.

Treatment Phase:

Once you have been randomly assigned to receive either ibudilast (MN-166) or placebo, the following assessments will be completed on **Study Days 1 through 7**:

- Ibudilast (MN-166) or placebo capsules will be given to you twice a day, once in the AM and once in the PM;
- A physical exam will be done
- Your oxygen use including CPAP, BiPAP, and nasal cannula will be measured;
- Your clinical status will be assessed;
- You will be asked questions about your general health;
- You will be asked if there was a change in your medication(s).

In addition, on Study Days 1, 3, 5 and 7**,** a 12-lead ECG will be done and a blood sample will be taken from a needle in your arm for routine, laboratory tests, biomarkers and pharmacokinetic samples to measure the amount of ibudilast in your blood. The total amount of blood that will be taken is estimated to be about 2 tablespoons (30 CC).

Study Day 14

The following assessments will be completed on Study Day 14:

- A physical exam will be done
- Your clinical status will be assessed using a brief questionnaire
- Your vital signs (blood pressure, heart rate, pulse, and temperature) will be taken
- Your oxygen use including CPAP, BiPAP, and nasal cannula will be measured;
- A blood sample to collect biomarkers and routine clinical labs (complete blood count and comprehensive metabolic panel) will be taken from a needle in your arm for routine laboratory tests and biomarkers (to measure inflammation in your body). The total amount of blood that will be taken will be about 2 tablespoons;
- You will be asked questions about your general health and any medications you may have taken

Study Day 28

The following assessments will be completed on Study Day 28:

- Your clinical status will be assessed using a brief questionnaire
- Your oxygen use including CPAP, BiPAP, and nasal cannula will be measured;
- You will be asked questions about your general health and any medications you may have taken

Study Day 60

The following assessments will be completed on Study Day 60:

- Your clinical status will be assessed using a brief questionnaire
- Your oxygen use including CPAP, BiPAP, and nasal cannula will be measured;
- You will be asked questions about your general health and any medications you may have taken

In addition, for subjects who are intubated (at screening or during the study the following will be done at Study Day 60:

- Vital signs (blood pressure, heart rate, pulse, and temperature)
- 12-lead ECG
- A blood sample will be taken for routine labs

If you are discharged from the hospital early, you will be given your study medication with instructions to take at home. You will also be given a pulse oximeter, a device to measure your oxygen levels, once a day up to Day 14. You do not need to return the device.

As a participant in this study, you have certain responsibilities to help ensure your safety. These responsibilities are listed below:

- Report all side effects and medical problems to the study personnel;
- Inform the study doctor or staff if you decide to discontinue your participation at which time you will be requested to complete the assessments that were scheduled on the last day of study treatment.

What are the risks associated with this study?

While participating in this research study, you are at risk for side effects. Your study doctor will discuss these with you. The treatment used in this study may cause all, some, or none of the side effects listed. There also may be other side effects that have not been reported. Other drugs may be given to manage side effects and make you more comfortable (such as for nausea or headache). Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious, or long-lasting.

The known side effects are:

Likely (occurring in more than 20% of people taking the drug)

- none

Less Likely (occurring in less than 5% of people taking the drug)

- appetite loss
- nausea

- diarrhea
- headache
- rash
- itching

Rare but serious (uncommon, between 1-10 out of 1000 people who have taken MN-166) elevated liver enzymes which can be an indication of liver damage.

Because this treatment is considered investigational and has not received FDA approval, there may be other risks that we do not know about at this time.

Risk of Allergic Reaction

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, which can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction or you are having trouble breathing, seek help from medical personnel right away.

Number of Subjects who took Ibudilast in Prior Clinical Trials

Approximately 750 people, including nearly 300 with multiple sclerosis (another serious neurological disease), 130 with progressive MS and nearly 50 with early ALS (ALS history within 5 years) have been treated with MN-166 in research studies. Generally, good safety and tolerability have been seen. The side effects that were seen in a 2-year study were gastrointestinal (meaning related to the stomach and intestines), and included nausea and diarrhea, and an increase in liver enzymes.

MN-166 has been given to nearly 300 patients with relapsing remitting multiple sclerosis. There were 20 serious adverse events (side effects) reported. Most of the serious adverse events were gastrointestinal in nature or having to do with bone fractures. All of these serious adverse events were considered by the study doctors to be unlikely or not related to MN-166. Six of the serious adverse events were considered severe and two were considered life-threatening. Nine subjects stopped the study due to a side effect. Two side effects (liver disorders) were possibly related to taking MN-166.

MN-166 was given to approximately 130 patients with progressive multiple sclerosis. There were 58 serious adverse events (31 in placebo group, 27 in MN-166 group) reported. Two serious adverse events were considered possibly related to study treatment: thrombocytopenia in the placebo group and ataxia in the MN-166 group.

MN-166 were given to nearly 50 subjects with early ALS patients (ALS history within 5 years). A total of 7 serious adverse events were reported in ALS patients. All of the serious adverse events were considered to be unlikely or unrelated to study drug by study doctor. Four of these

serious events were considered severe (dysphagia, ureteral stone, pneumonia and ankle fracture) and bowel obstruction was considered life-threatening.

As noted from the above-mentioned studies, gastrointestinal (GI) distress, which includes nausea and diarrhea, appears to be the most common side effect. The GI symptoms associated with MN-166 tend to occur early (within 1-2 weeks) and usually last for only a few days or weeks and then improve. These symptoms may be relieved with anti-diarrheal or anti-nausea drugs, if necessary. Usually, a majority of those receiving MN-166 recover from these symptoms within several days (with or without anti-diarrheal drugs). Talk to your study doctor if you experience these symptoms, particularly if they last for more than 2-3 weeks.

Other rare side effects associated with MN-166 are cold symptoms, itching sensation, rash, dizziness, tremors, insomnia (trouble sleeping), drowsiness, sudden blushing, anorexia (decreased appetite), abdominal pain, abdominal bloating, palpitations, flushed appearance, anemia (low red blood cell counts), low white blood cells, tiredness, facial edema (swelling), abnormal sound sensitivity (changes in your hearing) and metallic taste in your mouth.

Risks associated with blood drawing may include pain, bruising, and infection. Rarely, a person will faint.

Reproductive Risks

The effect of MN-166 on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be potentially harmful. Because of these unknown risks, if you are capable of giving birth to or fathering a child, you and your sexual partner should use adequate birth control measures while you are in this study. If you are a female who is sexually active and able to become pregnant, or a man with a sexual partner who is able to become pregnant, you must agree to use one or more of the birth control methods listed below. You must use birth control for the entire study and at least 30 days after your last dose of study drug. Acceptable birth control methods for this study are:

- Abstinence (no sex)
- Oral contraceptives (birth control pills)
- IUD (a small T-shaped device containing either copper or a hormone inserted into the womb for birth control)
- Diaphragm with spermicide (a foam, cream or gel that kills sperm)
- Norplant (birth control capsules that are inserted in the skin of the upper arm of a female)
- Approved hormone injections
- Condoms with spermicide
-

Women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a well-documented method of surgical sterilization (meaning hysterectomy or had your tubes tied/tubal ligation). All other female subjects must have a negative pregnancy test before starting the study drug.

If during the study you think you are pregnant, you must tell your study doctor and stop taking the study drug immediately. Your study doctor may ask you about the outcome of your pregnancy.

Men cannot take part in this study if they are actively trying to get their sexual partner pregnant. During this study if you think your partner is pregnant you must tell the study doctor immediately. Your study doctor may ask you about the outcome of your partner's pregnancy.

What if there are new findings about the study drug?

You will be told about any new information that might change your decision to take this experimental drug.

What are the possible benefits of taking part in this study?

There may be no direct clinical benefit from participating in this study. However, the information obtained from this study will be used by the Sponsor to determine the safety and tolerability of the study drug and may help in the future development of a new therapy for patients who are at risk for developing ARDS.

What will it cost me to take part in this study?

The cost of the study drug will be paid for by the sponsor, MediciNova. The cost for some of your tests may be billed to your insurance.

Can you choose to not participate or withdraw from the study without penalty or loss of benefits?

Your participation in this study is completely voluntary. You may refuse to participate or withdraw from the study at any time. If you refuse to participate or withdraw from the study, you will not be penalized or lose any benefits and your decision will not affect your relationship with your doctor or hospital.

However, if you decide to stop study participation, you are encouraged to talk with your doctor regarding safe removal from the study as described below. If you must be discontinued from the study prior to its completion, you will be asked to have a final assessment to evaluate your general health.

What alternatives are there if I do not want to take the experimental drug?

You do not have to participate in this study to receive treatment for your condition. The study doctor will discuss other treatment options with you, including any potential side effects or risks. If you decide not to take part in this study it will not affect your ability to receive medical care. You will be treated as per standard of care.

Does my doctor need my authorization to use and disclose my health information?

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. Your doctor must get your authorization (permission) to use or give out any health information that might identify you.

What about your confidentiality?

Research records will be kept confidential to the extent allowed by law. The records of this study will be kept private. In any kind of report published, we will not include any information that will make it possible to identify a patient. Under the terms specified in the Health Insurance Portability and Accountability Act of 1996 you have the right to privacy, and all information obtained in this clinical research study that can identify you will remain confidential to the greatest extent possible within state and federal laws. Your name will not be revealed in any reports or publications resulting from this study. The United States Food and Drug Administration (FDA), the Institutional Review Board (IRB), Sponsor and/or its designee (the study monitor), may inspect and copy your records pertaining to this study. The results of the study will be reported to the FDA and possibly other governmental agencies.

When FDA requires subject names, FDA will treat such information as confidential; however disclosure to third parties may be required on rare occasions. Therefore, absolute protection of confidentiality by FDA cannot be promised or implied. Every effort will be made to keep your personal information confidential.

What will happen to the results of this clinical study?

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This website will not include information that can identify you. At most, the web-site will include a summary of the results. You can search this website at any time.

The results of this study will be used to make informed clinical decisions for developing this new study drug. If you want the results to be made available to you, please talk to the study doctor. Results from clinical studies are often published in scientific journals, however, your personal information will remain confidential.

Will you be compensated for participating in this study?

You will not be paid to participate in this research study. However, you will be reimbursed for travel expenses, if applicable, when accompanied by receipts. Your study coordinator will discuss this with you.

Who may use and give out information about me?

Information about your health may be used and given to others by your doctor and staff. This may include information obtained both during and after the experimental treatment.

Who might get this information?

Anyone working for or with your doctor may have access to your medical and experimental drug treatment information.

Information about you and your health that might identify you may be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- The [**Name of Institutional Review Board**]
- MediciNova, Inc. (sponsor)

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be treated with the experimental drug.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by giving written notice to your doctor. If you withdraw your permission, you will not be able to continue taking the experimental drug.

When you withdraw your permission, no new health information that might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others.

What happens if I am hurt while taking Ibudilast?

If it is determined by Dr. Geoffrey Chupp that an injury occurred as a direct result of taking

Ibudilast, then you and/or your insurance will not have to pay for the cost of immediate medical care to treat the injury.

There are no plans to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care.

By signing this consent form, you will not give up any legal rights.

Who do I call if I have questions or concerns?

Contact Dr. XXX at **XXX-XXX-XXXX**, or Dr. Kazuko Matsuda, Chief Medical Officer at MediciNova (858-373-1500) for any of the following reasons:

- If you have any questions concerning your participation in this study;
- If at any time, you feel you have experienced a study-related injury or a reaction to the experimental drug and for information about how to receive treatment; or
- If you have questions, concerns or complaints about the study

If you have questions about your rights as a patient in this study or if you have questions, concerns or complaints about the study, you may contact:

[Name, address and contact information of Institutional Review Board)

Telephone:

E-mail:

[**Name of IRB**] is a group of people who independently review research, including single patient treatment plans.

[**Name of IRB**] will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact [**Name of IRB**] if your doctor or your doctor's staff cannot be reached or if you wish to talk to someone other than your doctor or doctor's staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to participate in this study, you will receive a signed and dated copy of this consent form for your records.

CONSENT

I have read the information in this consent (or it has been read to me). All my questions about this research study and my participation in it have been answered. I freely consent to participate in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

_____

Print [Name of Patient]

CONSENT SIGNATURES:

_____ _____

Signature of Patient Date

_____ _____

Signature of person obtaining consent Date

STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, Tolerability, Biomarkers and Pharmacokinetics of Ibudilast (MN-166) in COVID-19 Subjects at Risk for Developing Acute Respiratory Distress Syndrome

MN-166-COVID-19-201

Protocol Version: Amendment 2 (03 November 2020)

Protocol Version: Amendment 4 (31 March 2021)

	Name	Signature	Date
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Contributor:	Charles S Davis, PhD *Biostatistician* *CSD Biostatistics, Inc*	Charles S Davis	18 Aug 2022
Approved by:	Kazuko Matsuda, MD, PhD, MPH *Chief Medical Officer* *MediciNova, Inc.*		18-AUG-2022

Date: **August 18, 2022** **Version:** **2.0 (replaces SAP v1.0)**

HISTORY OF CHANGES

All versions of the document must be documented in the table of history of changes. The owner of this document must act in accordance with the latest version of the document.

Version	Effective Date	Change description
2.0	August 18, 2022	Section 1 Introduction • Age range was corrected to reflect protocol. • Discrepancies between protocol and SAP was addressed Section 2.2.3 Secondary Outcome Variables • Exploratory Analysis was described. Section 6 Analysis Population • Full Analysis Set was corrected Section 10.1. Primary Efficacy Variable Analysis • Nonresponders in the study were defined • A supportive analysis for each of the two co-primary endpoints will be conducted. Section 10.2 Secondary Efficacy Variable Analysis • Secondary endpoints that are defined as the change from baseline will be analyzed using analysis of covariance (ANCOVA) models
1.0	May 18, 2022	None: Initial Document

TABLE OF CONTENTS

ABBREVIATIONS

Acronyms, Abbreviations, Initials	Description / Explanation
AE	Adverse Event
ANOVA	analysis of variance
BS	Biostatistics
Cfb	Change from baseline
CRF	Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICH	The International Concil for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPF	Idiopathic Pulmonary Fibrosis
NA	Not Applicable
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
PM	Project Manager
PPS	Per Protocl Set
RA	Regulatory Authority
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SOP	Standard Operating Procedure
TESAE	Treatment Emergent Serious Adverse Event
TEAE	Treatment Emergent Adverse Event

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting MediciNova Inc. protocol MN-166-COVID-19-201, *A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, Tolerability, Biomarkers and PK of ibudilast (MN-166) in COVID-19 Participants at Risk for Developing Acute Respiratory Distress Syndrome.*

This phase 2 study is being completed to assess the safety, tolerability, and efficacy of MN-166 in male and female subjects 18 to 80 years of age, inclusive, who are hospitalized for complications from COVID-19 infection, are at risk for developing ARDS, and receive standard of care including anticoagulation. The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol MN-166-COVID-19-201, amendment 2 issued 01 November 2021 and amendment 4 issued 31 March 2021*
- Case report forms (CRFs) for Protocol MN-166-COVID-19-201.
- ICH E9: Guidance on Statistical Principles for Clinical Trials.
- ICH E3: Guideline for the format and content of the clinical and statistical sections of an application
- ICH E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

The SAP supplements the clinical protocol. Please refer to the clinical protocol for details on the rationale for the intervention, eligibility criteria, conduct of the trial, clinical assessments and the timing of their use in the trial, definitions and reporting of adverse events, data management conventions, and regulatory oversight and compliance procedures. In case of discrepancies between the SAP and the clinical protocol concerning matters of data analysis, the SAP is authoritative. On all other matters, the clinical protocol is authoritative.

**No subjects were consented under Protocol v.1.0, Amendment 1, and Amendment 3 because they were not submitted to the institutions' IRB.*

2 STUDY OBJECTIVE AND ENDPOIINTS

2.1 Study Objectives

2.1.1 Primary objectives

The primary objectives of the study are to evaluate:

- Efficacy of ibudilast vs. placebo in COVID-19 subjects measured by the proportion of subjects free of respiratory failure at Day 7
- Efficacy of ibudilast vs. placebo in COVID-19 subjects measured by clinical status at Day 7

2.1.2 Secondary Objectives

The secondary objectives of the study are to evaluate:

- Efficacy of ibudilast vs. placebo in COVID-19 subjects measured by the proportion of subjects free of respiratory failure at Days 14, 28 and 60 (in intubated subjects only)
- Efficacy of ibudilast vs, placebo in COVID-19 subjects measured by clinical status at Days 14, 28 and Day 60 (in intubated subjects only)
- Anti-inflammatory effects of ibudilast vs. placebo on cytokine levels
- Safety and tolerability of ibudilast vs. placebo in COVID-19 subjects
- Pharmacokinetics of ibudilast vs. placebo in COVID-19 subjects

2.2 Study Endpoints (Outcome Variables)

2.2.1 Co-Primary Outcome Variable(s)

The co-primary objectives of the study will be evaluated based on the following clinical measures:

- Proportion of subjects free from respiratory failure defined by free from supplemental oxygen requirements (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Day 7
- Proportion of subjects with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale and discharge record at Day 7

2.2.2 Secondary Outcome Variable(s)

- Proportion of subjects free from respiratory failure as defined by free from supplemental oxygen requirement (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Days 14, 28 and Day 60*
- Proportion of subjects with mechanical ventilation /intubation at Days 7, 14, 28 and Day 60*
- Changes from baseline in clinical status using the NAID 8-point ordinal scale and discharged record at Days 7, 14, 28 and 60*
- Proportion of subjects with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale and discharge record at Days 14, 28 and 60*
- All-cause mortality at Days 28and Day 60*
- Proportion of the subjects discharged from hospital at Days 7, 14, 28 and 60*
- Change from baseline in migration inhibitory factor (MIF), (interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), and C-reactive protein (CRP) at Day 3,5,7 and 14
- Incidence, frequency, and severity of adverse events at Day 7, 14, 28 and Day 60*
- Change from baseline of the following parameters at Days 7, 14 and Day 60*:
  - ALT
  - AST

- Serum creatinine
- BUN
- Complete blood count
- Total bilirubin
- D-dimer

- PK plasma concentrations and parameter (PK population)

*Intubated subjects only on Study Day 60

2.2.3 Exploratory Endpoints

Exploratory analysis not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analysis not identified in this SAP performed will be clearly identified in the respective CSR.

3 STUDY METHODS AND ENDPOINTS

3.1 Overall Study Design and Plan

This is a randomized (1:1), placebo-controlled, double-blind, parallel-group study of MN-166 (ibudilast) in hospitalized COVID-19 subjects at risk for developing ARDS receiving standard of care including anticoagulation. Approximately 40 participants are planned to be enrolled. The study will consist of a Screening Phase followed by a 7-days Double-blind Treatment (DBT) and Follow-up Phase. Following the Screening Phase, if the subject meets eligibility criteria, subject will be administered treatment with MN-166 (ibudilast) or placebo. Subjects will receive ibudilast 100 mg/d (50 mg b.i.d) or placebo every day for 7 days. The Follow-up phase is consisted of three visits: Day 14, Day 28, and Day 60 (subjects enrolled under amendment 4 only) post-baseline visit.

Subjects who are discharged prior to Day 7 will be given the remainder of their study medication to be taken at home and a pulse oximeter supplied by the sponsor to measure their O_2 levels once daily until Study Day 14.

Eligible participants will consist of males and females ranging in age from 21 to 80 years old, inclusive, who have SARS-CoV-2 infection confirmed by WHO criteria, chest abnormalities consistent with COVID-19 pneumonia, $SpO_2 \leq 92\%$ on room air, ≥24 BPM, and/or requirement of supplemental O_2.

Overall study design and plan is described in detail in Protocol Section 11.

3.2 Selection of Study Population

Inclusion and exclusion criteria are described in detail in Final Protocol Sections 12.2 and 12.3.

3.3 Method of Treatment Assignment and Randomization

During the Double-blind Treatment Phase, randomization occurred in a 1:1 ratio (MN-166: Placebo). The randomization scheme was generated by an independent statistician and sent to each site's unblinded pharmacist in a password protected file.

3.4 Treatment Masking (Blinding)

Participants and all personnel involved with the conduct and interpretation of the study, including the investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor and accessible only to authorized persons (e.g., unblinded pharmacist) until the database is locked

To ensure that treatment allocation remains concealed to both staff and participants, the following measures will be taken:

- Active drug and placebo will be identical in appearance
- Drug supplies to investigational pharmacy will be coded

4 SEQUENCE OF PLANNED ANALYSIS

4.1 Interim Analysis

There are no planned interim analyses for this study.

4.2 Data Monitoring Committee Meetings

Not applicable.

5 SAMPLE SIZE DETERMINATION

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 40 participants is deemed to be appropriate for this purpose.

6 ANALYSIS POPULATIONS

The following analysis populations are planned for the studies:

- **Full Analysis Set (FAS)** will include all randomized subjects.
- **Safety Analysis Set (SAS)** will include all randomized subjects who received at least one dose of study drug and had at least one post-dose safety assessment.
- **Per Protocol Analysis (PP):** will consist of the FAS subjects excluding those with major protocol violations.

- **Pharmacokinetic Population (PK):** will consist of the subjects for which PK collection was performed. Eight subjects are anticipated to participate in PK sample collection.

6.1 Use of analysis populations in different analyses

Safety analyses will be conducted on the Safety Analysis Set, and participants will be analyzed based on the treatment they received. Efficacy analysis will be conducted on the Full Analysis Set, and participants will be analyzed based on the treatment to which they were randomly assigned.

7 GENERAL ISSUES FOR STATISTICAL ANALYSIS

Data from all clinical assessments will be listed and, where appropriate, summarized by treatment arms using descriptive statistics. Summary (descriptive) statistics of continuous variables include n, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum values at each time-point. For categorical variables, the number and percent of counts will be presented.

7.1 Definition of Treatment Arms

Treatment arms will be denoted as follows in the TLFs:

- "MN-166" - 50 mg of MN-166 administered orally twice daily
- "Placebo" – Matching Placebo administered orally twice daily

7.2 Definition of Baseline

Unless otherwise specified, baseline is defined as the measurement closest to the date of the first administration of Investigational Medicinal Product (IMP) and preceding the first dose of IMP (MN-166 or Placebo).

7.3 Definition of Visit Windows

The same visit windows will be used as defined in the protocol.

- Screening visit (up to -3 days)
- Day 1 (baseline) (0 days)
- Days 2-7 (0 days)
- Day 14 (±3 days)
- Day 28 (±3 days)
- Day 60 (±7 days)

7.4 Multi-center Study

The study will be conducted at two centers:

Denver Health and Hospital Authority

Yale School of Medicine

7.5 Multiple Comparisons and Multiplicity

There are two co-primary endpoints. Because study success requires success on both, each will be tested using a one-sided alpha level value of 0.025 (equivalent to a two-sided alpha of 0.05). All other analyses will be conducted using one-sided tests at the alpha=0.025 level of significance, with no adjustment for multiplicity.

7.6 Planned Subgroup Analyses

No subgroup analyses are planned in this study.

7.7 Analysis Software

All analysis will be performed using SAS® Software version 9.4 or above.

7.8 Clinical Status Scale

In this trial, the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale is utilized to assess clinical status at Screening, Days 1-7, and on Days 14, 28, and 60 (for intubated subjects only). In Section 14.5 of the protocol, the numbers (1-8) are in reverse, where a higher number represents improvement, which is inconsistent with the official NIAID 8-point ordinal scale. The SAS programmer will correct the NIAID 8-point ordinal scale to reflect the official scale shown below.

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

8 STUDY PARTICIPANTS

8.1 Disposition of Participants and Withdrawals

All participants who provide informed consent will be accounted for in this study. The number of screen failures will be presented. The number and proportion of participants in each analysis set will be presented by treatment arm (in percentage of the number of

participants randomly assigned) and overall. The number and proportion of completers will be presented by treatment arm and overall. The number and proportion of early withdrawals will be presented by the coded term for main reason of withdrawal and overall, by treatment arm and overall.

Participants who are in the Safety Analysis Set but not in the Full Analysis Set will be listed. Randomization errors will be listed.

8.2 Protocol Deviations

The number and proportion of participants with protocol deviations will be presented by treatment arm, for each coded term.

All protocol deviations will be listed.

8.3 Inclusion and Exclusion Criteria

Participants who meet all the inclusion criteria and none of the exclusion criteria are eligible to participate in the clinical trial.

Deviations from inclusion/exclusion criteria will be listed.

9 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

9.1 Demographics

For variables assumed to be continuous, like age at screening, body weight and height descriptive statistics will be prepared by treatment arm, for each analysis set separately.

For categorical variables like gender, race, ethnicity, frequency tables (n and percentage) will be prepared by treatment arm, for each analysis set separately.

All demography data will be listed.

9.2 Prior and Concomitant Medications

Prior medications/therapies are defined as those for which the end date is prior to the date of first IMP administration. Concomitant medications/therapies are defined as those with start date on or after the date of first IMP administration and those with start date prior to the first IMP use but with end date on or after the date of first IMP administration.

Concomitant medications in the database will be coded using the most recent version of the World Health Organization Drug Dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system. The number and percentage of participants who took prior and concomitant medications will be summarized separately by ATC classification first level (alphabetically), ATC classification second level (in decreasing order of frequency) and treatment arm.

These therapeutics will be listed by subject along with their classification, indication of the treatment, total daily dose and start and stop date of the treatment.

The number and percentage of participants who took prior and concomitant treatments will be presented separately.

All prior and concomitant medication data will be listed.

9.3 Baseline and Screening Conditions

Baseline and Screening condition data will be assessed by treatment arm using descriptive statistics. No inferential test statistics are planned for baseline comparison of the treatment arms.

9.3.1 Baseline Medical History

All medical history records will be coded according to the latest version od MedDRA and summarized by system organ class and preferred term. The number and percentage of participants in different medical history categories will be presented by treatment arm.

10 EFFICACY ANALYSIS

Efficacy analysis will be performed on the Full Analysis Set. All efficacy measurements will be listed.

10.1 Primary Efficacy Variable Analysis

The co-primary efficacy endpoints are listed below. The primary analysis for each of these two endpoints will be conducted using Pearson's chi-square tests. Because study success is defined as success on both, each of the two co-primary endpoints will be tested using a one-sided significance level of 0.025.

- Proportion of subjects free from respiratory failure
    - Calculate the proportion of the subjects free from supplemental oxygen (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, ECMO, CPAP, BiPAP, nasal cannula) at Day 7
- Proportion of subjects with improvement in clinical status using the NIAID 8-point ordinal scale and discharge record at Day 7
    - Calculate the proportion of the subjects who improved at least one-point from baseline

For each of the two co-primary endpoints, subjects whose response status is unknown will be assumed to be nonresponders.

A supportive analysis for each of the two co-primary endpoints will be conducted using the Mantel-Haenszel test stratified by the randomization stratification variable (use of IL-6 antibody therapy).

10.2 Secondary Efficacy Variable Analysis

The secondary efficacy endpoints are the following:

- Proportion of subjects free from respiratory failure as defined by free from supplemental oxygen requirement (invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO, CPAP, BiPAP, nasal cannula) at Days14, 28 and Day 60* Proportion of subjects with mechanical ventilation /intubation at Days 7, 14, 28 and Day 60*
- Change from baseline in clinical status using NIAID 8-point scale and discharge record at Days 7, 14, 28 and 60* Proportion of subjects with at least a one-point improvement in clinical status using the NIAID 8-point ordinal scale and discharge record at Day 14,28 and 60*
- All-cause mortality at Days 28 and Day 60* Proportion of the subjects discharged from hospital at Day 7,14, 28 and 60*
- Change from baseline in migration inhibitory factor (MIF), (interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), and C-reactive protein (CRP) at Day 3, 5, 7 and 14

*Intubated subjects only on Study Day 60

All secondary endpoints that are defined as proportion variables will be analyzed using Pearson's chi-square tests. Secondary endpoints that are defined as the change from baseline will be analyzed using analysis of covariance (ANCOVA) models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate. All secondary analyses will be conducted using one-sided tests at the alpha=0.025 level of significance, with no adjustments for multiplicity.

10.3 Exploratory Analysis

Time to discharge

10.4 Pharmacokinetics Analysis

Pharmacokinetic analyses will be performed on plasma samples from eight subjects. Blood samples (approximately 2 mL per sample) will be collected at each time point for the bioanalytical assay of MN-166 and stored frozen at approximately -80°C until shipment is sent to the PK vendor. Blood samples will be assayed for MN-166 using a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method.

10.4.1 Pharmacokinetic Samples

Pharmacokinetic samples will be collected on Day 1: AM Predose, and at 2, 4, 8 and 12 hours (Predose of PM dose), and on Day 3 and Day 5 at AM Predose.

10.4.2 Pharmacokinetic Parameters

The following PK parameters will be calculated using model-independent approaches (NCA) from MN-166 individual plasma concentrations, whenever practical.

Parameter	Description of Parameter
t_{max}	Time from the start of dosing at which the maximum concentration was observed
C_{max}	Maximum observed concentration
AUC_{0-t}	Area under the concentration versus time curve from the start of dose administration to the last quantifiable point within the dosing interval
λ_z	Terminal rate constant calculated from the terminal slope of the log-linear regression of concentration with time
$t_{1/2}$	Terminal half-life, calculated as ln(2)/ λ_z
$AUC_{0-\infty}$	Area under the concentration versus time curve from time 0 to infinity calculated as AUC0-t + Clast/λz, where Clast is the last quantifiable concentration
CL or CL/F	Total body clearance, calculated as Dose/ $AUC_{0-(}$
V_z or V_z/F	Terminal volume of distribution, calculated as CL/λ_z

11 SAFETY AND TOLERABILITY ANALYSIS

All safety analyses will be performed for participants in the safety analysis set.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Treatment Emergent Adverse Events:
  - Clinical laboratory Treatment Emergent Adverse Events
  - Discontinuation due to TEAEs
  - Treatment Emergent Serious Adverse Events
- Pregnancies (if any reported)
- Clinical Laboratory Investigations
- Vital Signs
- Physical examinations

11.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 25.0.

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of MN-166), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness. If it cannot be determined whether the AE is treatment emergent due to a partial onset date then it will be counted as such.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to study discontinuation or death by MedDRA system organ class and preferred term.

As this is a double-blind study, the causality assessment should be made under the assumption that the subject is receiving active study medication. If considering unblinding, this assessment should be made prior to unblinding to avoid bias.

11.1.1 All Adverse Events

An overview of number of participants (%) with treatment-emergent AEs will be presented for the main AE categories (All AEs, AEs leading to discontinuation, SAEs, SAEs leading to discontinuation, AEs with at least Grade 3 severity (Severe AEs, Life-threatening AEs, Deaths), AEs and SAEs with relationship to IMP as possibly related, probably related, or related) by treatment arm and phase.

11.1.2 Adverse Events Leading to Withdrawal

A data listing of AEs leading to withdrawal will be provided, displaying details of the event(s) captured on the CRF.

11.1.3 Serious Adverse Events

A data listing of SAEs will be provided, displaying details of the event(s) captured on the CRF. Serious adverse event narratives will be provided for the CSR by MediciNova.

11.1.4 Deaths

If any subject dies during the study, relevant information will be supplied in a data listing, and appropriate SAE narratives.

11.2 Pregnancies

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Participants are to be discontinued from the study if they become pregnant.

11.3 Clinical Laboratory Evaluations

Changes from baseline in laboratory values will be summarized by treatment groups for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed by treatment groups. Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed. Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated by treatment group. Baseline is defined as the last non-missing value prior to the start of study drug infusion.

11.4 Electrocardiogram (ECG)

Descriptive statistics will be presented for ECG measures of PR interval, QRSD interval, QT interval, QTc interval (Fridericia's method), and HR. These statistics will be presented by treatment arm, phase and visit.

The number and percentage of subjects with normal and abnormal ECG results will be summarized by treatment arm, phase, and visit. All ECG measurements will be listed.

11.5 Vital Signs

Changes in vital signs from baseline to each visit will be summarized by treatment groups.

11.6 Physical examination

Physical examination results will be included in data listings only.

12 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
3. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York, NY: Marcel Dekker; 1982.
4. Gough K, Hutchinson M, Keene O, Byrom B, Ellis S, Lacey L et al. Assessment of dose proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK joint working party. Drug Information Journal 1995; 29: 1039-1048.
5. Emergent Product Development Gaithersburg Inc. Randomized, double-blind, placebo-controlled, parallel group, single ascending dose study to determine the safety, tolerability and pharmacokinetics of UV-4B solution administered orally in healthy subjects. Clinical Report for Study ID 13-0001 issued 07 July 2016.

13 APPENDICES

13.1 Schedule of Assessments (Amendment 2)

Phase	Screening	Double-Blind Treatment Phase [d,f]							Follow-up	
Study Day	Day -3	Day 1 BL	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14[d] (± 3)	Day 28 (+/-3)
Informed consent	X									
Inclusion/exclusion criteria review	X									
Brief physical exam	X	X		X		X		X	X	
Clinical status using NIAID scale	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, RR, HR, Temp)	X	X	X	X	X	X	X	X	X	
O_2 therapy status and SpO_2	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X[a]		X[a]		X[a]		X[a]		
Biomarker plasma samples: MIF, IL-1β, IL-6, TNF-α	X	X		X		X		X	X	
PK blood sample[b]		X		X		X				
CBC, CMP, CRP, D-dimer, PT, INR	X[c]	X		X		X		X	X	
Randomize[e]	X									
Administer study drug		X	X	X	X	X	X	X		
Adverse event review		X	X	X	X	X	X	X	X	
Prior/Concomitant medication review	X	X	X	X	X	X	X	X	X	
Record survival status										X

[a] 12-lead ECG to be done between 2-4 hours after AM dose.
[b] Collect PK samples on Day 1 in the AM prior to study drug dosing and at 2, 4, 8, and 12 hours (Predose of PM dose); Day 3 and Day 5 prior to AM study drug dosing. PK samples to be collected for 8 subjects only.
[c] Serum β-hCG for pre-menopausal women.
[d] Telephone follow-up if subject is not in hospital. If subject is no longer hospitalized or cannot return due to COVID restrictions, a telephone follow-up to record O_2 usage/levels, AEs and conmeds may be conducted. All other assessments are optional.
[e] Subjects may be randomized during the Screening Phase after all of the screening assessments are completed and subject is considered eligible for the study or on Day 1.
[f] If subject prematurely discontinues from the study or is discharged from the hospital on Days 2, 4, or 6 collect biomarker samples in addition to other scheduled assessments. If subject prematurely discontinues from the study or is discharged on Days 1, 3, 5, or 7, conduct the study assessments scheduled on those days.
[g] Thirty-one (31) subjects were consented under Protocol amendment 2.

13.2 Schedule of Assessments (Amendment 4)

Phase	Screening	Double-Blind Treatment Phase [e,g]							Follow-up		
Study Day	Day -3	Day 1 BL	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14[e] (± 3)	Day 28 (±3)	Day 60 (±7)
Informed consent	X										
Inclusion/exclusion criteria review	X										
Brief physical exam	X	X		X		X		X	X		
Clinical status using NIAID scale	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, RR, HR, Temp)	X	X	X	X	X	X	X	X	X		X[i]
O_2 therapy status and SpO_2	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X[a]		X[a]		X[a]		X[a]			X[i]
Biomarker plasma samples: MIF, IL-1β, IL-6, TNF-α	X[b]	X		X		X		X	X		
PK blood sample[c]		X		X		X					
CBC, CMP, CRP, D-dimer, PT, INR	X[d]	X		X		X		X	X		X[i]
Randomize [f]	X										
Administer study drug		X [h]	X	X	X	X	X	X			
Adverse event review		X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Record survival status[j]									X	X	X

[a] 12-lead ECG to be done between 2-4 hours after AM dose.
[b] Biomarker blood sample collection at screening is optional if Screening and Day 1 assessments occur on the same day.
[c] Collect PK samples on Day 1 in the AM prior to study drug dosing and at 2, 4, 8, and 12 hours (Predose of PM dose); Day 3 and Day 5 prior to AM study drug dosing. PK samples to be collected for 8 subjects only.
[d] Serum β-hCG for pre-menopausal women.
[e] Telephone follow-up if subject is not in hospital. If subject is no longer hospitalized or cannot return due to COVID restrictions, a telephone follow-up to record O_2 usage/levels, AEs and conmeds may be conducted. All other assessments are optional.
[f] Subjects may be randomized during the Screening Phase after all of the screening assessments are completed and subject is considered eligible for the study or on Day 1.
[g] If subject prematurely discontinues from the study or is discharged from the hospital on Days 2, 4, or 6 collect biomarkers samples in addition to other scheduled assessments. If subject prematurely discontinues from the study or is discharged on Days 1, 3, 5, or 7, conduct the study assessments scheduled on those days.
[h] The first dose of study drug may be started in the AM or the PM.
[i] Vital signs, ECG and safety labs will be done in intubated subjects only.
Survival status is captured on the NIAID questionnaire.
[k] Five (5) subjects were consented under Amendment 4.

13.3 List of Tables

Table Number	Table Description
14.1	**Demographic Data**
14.1.1	Subject Disposition (including discontinued subjects)
14.1.2	Summary of Protocol Deviations
14.1.3	Demographics and Baseline Characteristics
	Summary of Disease Characteristics at Baseline by Treatment
14.1.4	Summary of Medical History
14.1.5	Prior and Concomitant Medications (Safety Population)
14.1.6	Study Drug Exposure
14.2	**Efficacy**
14.2.1	Number (%) of subjects free from respiratory failure at Day 7
14.2.2	Number (%) of subjects with at least a 1-point improvement in clinical status using the NIAID 8-point ordinal scale at Day 7
14.2.3	Number (%) of subjects free from respiratory failure at Days 14, 28, and 60
14.2.4	Number (%) of subjects with mechanical ventilation/intubation at Days 7, 14, 28, and 60
14.2.5	Change from baseline in clinical status using the NIAID 8-point ordinal scale at Days 7, 14, 28, and 60
14.2.6	Number (%) of subjects with at least a 1-point improvement in clinical status using the NIAID 8-point ordinal scale at Days 14, 28, and 60
14.2.7	Number (%) of subjects discharged from hospital at Days 7, 14, 28, and 60
14.2.8	All-cause mortality at Days 28 and 60
14.3	**Safety**
14.3.1	Summary of Treatment-emergent adverse events by Treatment
14.3.1.1	Incidence of TEAEs MedDRA System Organ Class and Preferred Term by Treatment
14.3.1.2	Incidence of TEAEs Occurring in more than 5% of Subjects by Treatment
14.3.1.3	Incidence of Post-treatment AEs by Treatment
14.3.1.4	Incidence of TEAEs by MedDRA System Organ Class, Preferred Term and Severity
14.3.1.5	Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Relationship to Study Drug
14.3.1.6	Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Relationship to Study Drug, and Severity
14.3.2	Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
14.3.3	Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Severity
14.3.4	Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Severity
14.3.4.1	Incidence of Subjects with Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Relationship
14.3.4.2	Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Relationship
14.3.4.3	Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Relationship and Severity
14.3.4.4	Incidence of TEAEs Leading to Early Termination by Treatment

14.3.4.5	Incidence of Deaths by Treatment
14.3.4.6	Incidence of TEAEs by Maximum Severity by Treatment
14.3.4.7	Summary of Clinical Laboratory Data: Clinical Chemistry by Treatment
14.3.4.8	Summary of Clinical Laboratory Data: Clinical Hematology by Treatment
14.3.4.9	Shifts from Baseline of Clinical Laboratory Data: Clinical Chemistry – Shift from Baseline to the Last Visit
14.3.4.10	Shifts from Baseline of Clinical Laboratory Data: Clinical Hematology by Treatment

13.4 List of Listings

Listing Number	Listing Description
16.2	**Subject Data Listings**
16.2.1	Analysis Populations and Treatment
16.2.1.1	Subject Disposition
16.2.1.2	Inclusion/Exclusion Criteria
16.2.2	Protocol Deviations
16.2.2.1	Major and Minor Protocol Deviations
16.2.2.3	Randomization Errors
16.2.3.1	Demographics and Other Baseline Characteristics
16.2.4	Prior, Concomitant, and Post-treatment Medications
16.2.4.1	Medical History
16.2.5	Study Drug Exposure
16.2.5.1	Drug Accountability and Compliance
16.2.5.2	Investigator Dose Optimization
14.2.5.3	Dose Interruptions
16.2.6	Individual Response Efficacy
16.2.6.1	NIAID clinical status 8-point ordinal scale
16.2.6.2	O2 assessment including invasive mechanical ventilation, non-invasive ventilation (CPAP, BiPAP, nasal cannula high-flow oxygen), or ECMO and SpO2
16.2.6.3	Day of Hospital Discharge
16.2.6.4	Survival Status
16.2.7	Individual Safety
16.2.7.1	Adverse Events
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16.2.8	Listing of Individual Laboratory Measurements by Subject, when Required by Regulatory Authorities
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16.2.8.3	Pregnancy Tests
16.2.8.4	Vital Signs
16.2.8.5	Electrocardiogram, Site Interpretation
16.2.8.6	Electrocardiogram, Central Reader Interpretation
16.2.8.7	Physical Examination