A Pilot Study to Assess the Safety, Tolerability and Efficacy of Selectin Inhibitor Uproleselan (GMI-1271) in Patients with COVID-19 Pneumonia

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Study Drug: **Uproleselan (**GMI-1271) injection, 50 mg/mL

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LIST OF TABLES

ABBREVIATIONS

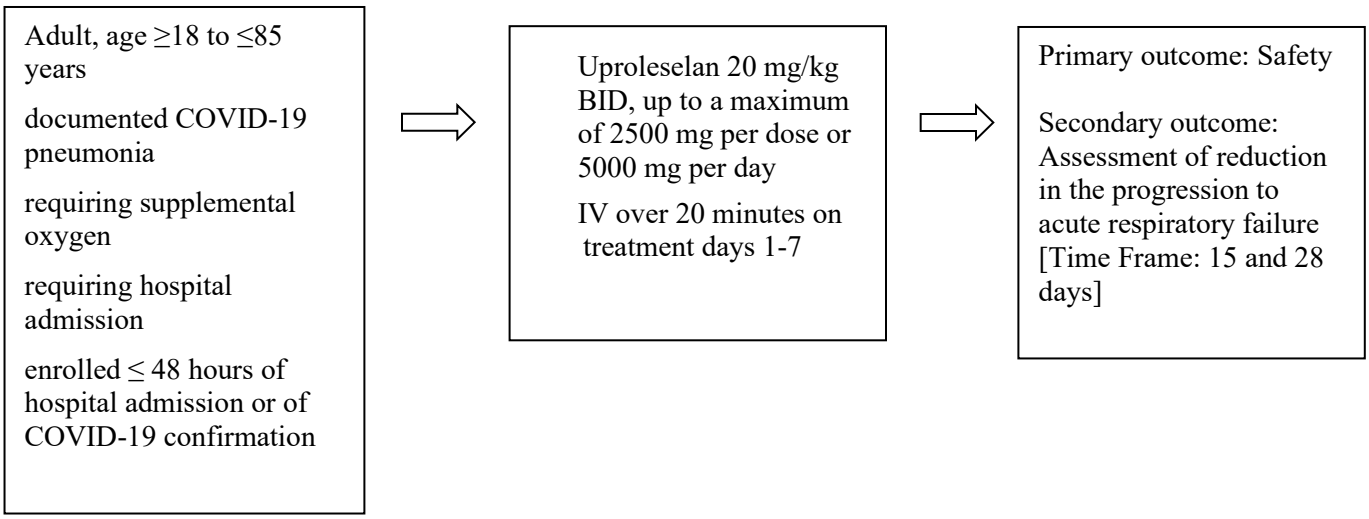
AC	Anticoagulation
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	Antithrombin III
AUC	Area under the curve
BD	Becton, Dickinson and Company
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BT	Bleeding time
BUN	Blood urea nitrogen
C or °C	Celsius
Cmax	maximum serum concentration
Cmin	minimum serum concentration
CBC	Complete blood count
CL_r	Renal clearance
CMP	Comprehensive metabolic panel
CrCl	Creatinine clearance
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
CRF	Case report form
CRO	Contract research organization
CSM	Clinical supply management
CTEP	Cancer therapy education program
CTO	Clinical trials office
DLT	Dose Limiting Toxicity
DHEP	di-(2-ethylhexyl) phthalate
DNA	deoxyribonucleic acid
DOACs	Direct oral anticoagulants
DSMB	Data and safety monitoring board

DSMC	Data and Safety Monitoring Committee
DSMP	Data and safety monitoring plan
DVT	Deep vein thrombosis
DVU	Diagnostic Vascular Unit
ECG	Electrocardiogram
ED	Early Discontinuation
EDTA	Ethylenediaminetetraacetic acid
EGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
ESL-1	E-Selectin Ligand-1
F or °F	Fahrenheit
F1.2	Prothrombin fragment 1+2
FDA	Food and Drug Administration
FSC	Forward scattered light
G or g	Grams
GCP	Good clinical practice
GMI	GlycoMimetics
H&P	History and physical examination
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
HSCs	Hematopoietic stem cells
IB	Investigator's Brochure
ICF	Informed consent form
ICF	International conference of harmonization
ID	Intraduodenal
IDS	Investigational Drug Service
IL-6	Interleukin-6
IL-10	Interleukin-10
IND	Investigational New Drug
INR	International normalized ratio
IP	Intraperitoneal
IRB	Institutional review board
ISTH	International Society of Thrombosis and Hemostasis
IU	International unit
IUD	Intrauterine device
IV or iv	Intravenous
KG or kg	Kilogram

LE	Lower extremity
LFA-1	Leukocyte function-associated antigen-1
LFTs	Liver function tests
LMWH	Low molecular weight heparin
m^2	squared
MAC-1	macrophage-1 antigen; CD11b/CD18
MAD	multiple ascending dose
MCRU	Michigan Clinical Research Unit
MICHR	Michigan Institute for Clinical Studies and Health Research
mg	Milligrams
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
Min	Minutes
MPs	Microparticles
MPO	Myeloperoxidase
MTD	Maximally tolerated dose
N	Number
NCI	National cancer institute
NETs	Neutrophil endothelial traps
ng	Nanogram
NHP	Non-human primates
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
PBS	Phosphate buffered saline
PE	Pulmonary embolism
pg	Picogram
PI	Principal investigator
PK	Pharmacokinetics
PMA	Platelet monocyte aggregates
PMNs	Polymorphonuclear leukocytes
PSGL-1	P-Selectin Glycoprotein Ligand 1
PT	Prothrombin time
PTS	Post thrombotic syndrome
QD	Daily
rpm	Revolutions per minute

SAE	Serious Adverse Event
SCD	Sickle Cell Disease
sCD40L	Soluble CD40L
SDF-1	Stromal cell-derived factor 1
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
sICAM-1	Soluble intercellular cell adhesion molecule 1
sLe^x	$SialyLewis^x$
sEsel	Soluble E-selectin
sPsel	Soluble P-selectin
SQ or SC	Subcutaneous
SSC	Side scattered light
sTF	Soluble tissue factor
TAT	Thrombin-Antithrombin Complex
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TEG	Thromboelastography
TF	Tissue factor
TNF-α	Tumor necrosis factor
TK	Toxicokinetics
Tx	Treatment
ULN	Upper limit of normal
UM	University of Michigan
US	United States
VTE	Venous thromboembolic disease
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolic disease
VWF	von Willebrand factor
WBC	White blood cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	A Pilot Study to Assess the Safety, Tolerability and Efficacy of Selectin Inhibitor Uproleselan (GMI-1271) in Patients with COVID-19 pneumonia
Phase	Phase I (proof of concept, prospective, interventional, open label single group assignment)
Methodology	Open label with matched de-identified retrospective control cohort
Study Duration	Approximately 24 months
Study Center(s)	Single Center in the United States – University of Michigan, Ann Arbor
Objectives	**Primary Objective:** Safety of uproleselan in patients with severe COVID-19 pneumonia. **Secondary Objectives:** To evaluate if treatment with uproleselan administered intravenously in addition to the best available therapy according to institutional guidelines is able to reduce the progression of acute respiratory failure, in patients with severe COVID-19 pneumonia. ● To evaluate overall survival and all-cause mortality at day 15 and 28. ● To evaluate changes in the COVID ordinal outcomes scale. ● To assess adverse events to evaluate the safety of uproleselan. ● To assess ventilator-free days, ICU-free days, oxygen, vasopressor free days. ● To evaluate changes in D-dimer. **Exploratory Objectives:** • To examine the correlation of plasma soluble E-selectin concentrations with clinical outcomes. • To examine the correlations of other biomarkers of interest with clinical outcome.
Number of Subjects	15 subjects will be enrolled in the experimental cohort to receive uproleselan. with 1:1 matched de-identified retrospective control cohort. (n=15)
Inclusion Criteria	1. Adults, ages 18 – 85 years. 2. Willing and able to provide informed consent prior to performing study procedures unless they have a legally authorized representative (LAR). 3. Documented COVID-19 pneumonia: defined as upper respiratory tract specimen (nasopharyngeal swab (NPS) or viral throat swab) positive for COVID-19 and imaging (CXR/CT scan) suggestive of COVID-19 pneumonia. 4. Confirmed coronavirus (SARS-CoV-2) infection, enrolled ≤ 48 hours of beginning oxygen need for COVID-19+ confirmed hospital admission.

	5. Currently hospitalized requiring supplemental oxygen. 6. Have severe COVID-19 according to the World Health Organization (WHO) Interim Guidance with confirmation by real-time RT-PCR assay. The enrollment criteria with one of the following: respiratory distress, respiratory rate (RR) ≥30 beats/min; oxygen saturation level less than 93% in resting state; or partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg. WHO, Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: Interim guidance. https://www. who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infectionwhen-novel-coronavirus-(ncov)-infection-is-suspected. 7. Willing and able to participate in all required evaluations and procedures.
Exclusion Criteria	1. In the opinion of at least one investigator, unlikely to survive for >48 hours from screening. 2. Severe chronic respiratory disease (e.g. COPD or other) requiring supplemental oxygen and/or having required mechanical ventilation pre-COVID-19 infection. 3. Concurrent enrollment in a COVID-related interventional drug trial. Use of remdesivir, steroids, and convalescent plasma are permitted along with other standard of care therapies for COVID. 4. Currently on invasive mechanical ventilation. 5. Hypotension defined as systolic blood pressure < 90 mmHg on two sequential readings at least 4 hours apart. 6. Total Bilirubin ≥ 3 x upper limit of normal (ULN), Creatinine Clearance ≤ 30 mL/min/1.73m^2. 7. Pregnant or breastfeeding. 8. Known diagnosis of an acute thrombosis on admission. 9. Concurrent dual antithrombotic therapy (aspirin or P2Y12 inhibitor plus anticoagulation to treat deep venous thrombosis or pulmonary embolism (single antiplatelet or anticoagulant agent at prophylactic dose is permitted). 10. Concomitant use of thrombolytic therapy. 11. Concomitant therapeutic systemic anticoagulant therapy (e.g. heparin, warfarin, direct thrombin inhibitors and direct factor Xa inhibitors). 12. History of recent major bleeding, defined in accordance with the criteria of the International Society on Thrombosis and Hemostasis (ISTH). 13. History of bleeding disorder thought to impose excessive bleeding risk, as per investigator discretion. 14. Hemodynamic instability, defined as inability to maintain mean arterial pressure. 15. Hypersensitivity to the active substance or to any of the excipients of uproleselan.

	16. Any physical examination findings and/or history of any illness that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study.
Study Product(s), Dose, Route	**Uproleselan** 20mg/kg BID, up to a maximum dose of 2500mg, IV infused over 20 minutes on days 1-7.
Duration of Administration	**Uproleselan**: 20-minute IV infusion BID on days 1-7.
Control	1:1 matched de-identified retrospective control cohort (patients enrolled during the same period with similar severity, not enrolled in another interventional trial, receiving best available therapy according to institutional guidelines).
Statistical Methodology	This is a pilot proof of concept feasibility study. 15 patients who consent to drug administration will be enrolled in the treatment arm. The sample size determination was not based on statistical power analysis but is large enough to provide adequate information regarding safety, and will contribute to the design of subsequent studies, and is the number of patients that we can expect to accrue in the current setting of the SARS-CoV2 pandemic. Descriptive statistics will be calculated for quantitative safety data, as well as change from baseline. Frequency counts will be compiled for classification of qualitative safety data. Regarding secondary endpoints, the efficacy of uproleselan in prevention of acute respiratory failure, the rate will be calculated as the proportion of patients who experienced at least one of the events above by day+15 from treatment start. The biomarkers will be evaluated for trends at the sample collection time points and contrasted graphically and with simple statistics to the levels observed for control cohort subjects, as the study is not powered for this endpoint.

1 BACKGROUND AND RATIONALE

1.1 COVID-19 Pneumonia and ARDS Disease Background

Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus (SARS-CoV2), is a highly infectious pathogen that spreads primarily through respiratory droplets and/or aerosol particles. Though many affected patients express only mild symptomatology, with fever, cough and myalgias/fatigue, approximately 10-20% of patients may develop a more severe phenotype with rapid progression to acute respiratory distress syndrome (ARDS), septic shock, disseminated intravascular coagulation (DIC) and hypercoagulability. Older age and co-morbid conditions (obesity, diabetes, immunocompromised, etc.) are known risk factors for a more severe disease phenotype. ARDS has a very high associated mortality rate.

ARDS causes diffuse alveolar damage in the lung.[1] There is hyaline membrane formation in the alveoli in the acute stage, and this is followed by interstitial widening and by edema and then fibroblast proliferation in the organizing stage. COVID-19 ARDS causes the typical ARDS pathological changes of diffuse alveolar damage in the lung.[2]

Pulmonary thrombosis is common in COVID-19 ARDS.[3] Coagulation dysfunction appears to be common in COVID-19 and is detected by elevated D-dimer levels. In fatal cases there is diffuse microvascular thrombosis, suggesting a thrombotic microangiopathy, and most deaths from COVID-19 ARDS have evidence of thrombotic disseminated intravascular coagulation.[4] This may explain some of the atypical or unexpected manifestations seen in the lung, such as dilated pulmonary vessels on chest CT, and episodes of pleuritic pain. Vascular enlargement is rarely reported in typical ARDS, yet was seen in most cases of COVID-19 ARDS.[5]

COVID-19 ARDS appears to have worse outcomes than ARDS from other causes. The intensive care unit and hospital mortality from typical ARDS are 35.3% (95% CI, 33.3–37.2%) and 40.0% (95% CI, 38.1–42.1%), respectively.[6] For COVID-19 ARDS, mortality ranged between 26% and 61.5% if ever admitted into a critical care setting, and in patients who received mechanical ventilation, the mortality can range between 65.7% to 94%. Risk factors for poor outcomes include older age; presence of comorbidities such as hypertension, cardiovascular disease and diabetes mellitus; lower lymphocyte counts; kidney injury; and raised D-dimer levels. Death from COVID-19 ARDS is due to respiratory failure (53%), respiratory failure combined with cardiac failure (33%), myocardial damage and circulatory failure (7%), or death from an unknown cause.[7]

Given the high mortality rate associated with COVID-19 ARDS, preventing progression of COVID-19 pneumonia in patients simply requiring supplemental oxygen to COVID-19 ARDS is a key priority and goal.

1.2 Selectins and COVID-19 Background

Cell Mediated Inflammation and COVID-19

The usual cause of death and the need for ventilator-assisted hospitalization from COVID-19 is the progression to ARDS, with an influx of neutrophils (PMN) into the lungs after extravasation from the bloodstream. These PMNs degranulate and then release a wide variety of inflammatory mediators. This results in a positive feedback loop with a further influx of PMNs, vascular leakage, fluid accumulation in the lungs, and impairment of oxygen exchange. Neutrophil and platelet accumulation in the alveolar space results in thrombo-inflammation, and platelets trigger release of neutrophil extracellular traps (NETs), which have been found to correlate with alveolar-capillary and epithelial barrier disruption in ARDS.[8] Amongst patients with severe SARS-CoV-2 viral pneumonia with progression to respiratory failure, serum cell-free DNA, myeloperoxidase (MPO)-DNA, and citrullinated histone H_3 (Cit-H_3) are elevated, highly specific markers of NETs. Neutrophil counts correlate with cell-free DNA and MPO-DNA.[9] Cell-free DNA and MPO-DNA levels were higher in hospitalized patients receiving mechanical ventilation as compared to hospitalized patients breathing room air, suggesting that illness severity is associated with neutrophil response.[9]

Additionally, in experiments performed *in vitro*, serum from SARS-CoV-2 infected patients triggered NET release from normal neutrophils.[9] A retrospective case control study of hospitalized COVID-19 patients reported that those who developed thrombosis had significantly higher blood levels of remnants of NETs (cell-free DNA, MPO-DNA complexes and citrullinated histone H_3) and neutrophil activation (as evidenced by elevated calprotectin) compared to those without thrombosis, and were associated with levels of D-dimer.[10] These data provide evidence that SARS-CoV-2 infection induces a pro-NETotic state amongst hospitalized patients, and these NETs could be partially responsible for the heightened thrombotic phenotype seen in these patients.

In addition to neutrophils, pathologic studies have also demonstrated a low to moderate number of mononuclear cells in the lungs in COVID-19 non-survivors.[11] The role they directly play is not entirely clear, but is likely multifactorial based on the diverse roles monocytes and macrophages (Mo/MΦ) play in lung physiology. Patients may manifest a significant cytokine storm with severe COVID-19 pneumonia that can lead to death[12, 13] and many of the responsible mediators are Mo/MΦ-derived.[14-16] These include proinflammatory cytokines such as interleukin (IL)-1β, IL-8, IL-6, and type I interferons (IFN-I). Direct viral infection may then promote the release from alveolar epithelial cells, alveolar macrophages and stromal cells of monocyte chemoattractants, resulting in a sustained recruitment of monocytes into the lungs.[17] These monocytes then differentiate into pro-inflammatory macrophages. Mo/Mϕ also activate and are activated by NK cells and T cells, further promoting this recruitment by granulocyte-macrophage-colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF), and interferon-γ (IFNγ).[17, 18] In the lungs, oxidized phospholipids can accumulate and they also activate these Mo/Mϕ. Virus sensing pathways such as toll-like receptor 7 (TLR7), sensing single-stranded RNA recognition, and Type 1 interferon may induce the expression of entry receptors allowing the virus to enter into the cytoplasm of the macrophages, activating the NLRP3 inflammasome.[17] This leads to the secretion of mature IL-1β and IL-18, which amplify macrophage activation through paracrine or

autocrine effects. Oxidative stress, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) also activate Mo/MΦ via TLR4-TRIF-TRAF6-NFκβ pathway, resulting in surface tissue factor expression.[17, 19] Additionally, activated neutrophils and Mo/Mϕ can directly bind to platelets, and these induce and amplify thrombosis.

Endothelial cell dysfunction has been reported to be very important in COVID-19 associated vascular inflammation and coagulopathy. Type 1 endothelial cell activation leads to the release of stored proteins such as P-selectin and vWF, while Type II endothelial cell activation occurs with the release of new proteins such as E-selectin, ICAM-1, VCAM-1, vWF, IL-1, MCP-1, and tissue factor.[20] At this phase, the processes are reversible but if left unchecked, endothelial cell apoptosis and even endothelial cell necrosis can occur, resulting in the impaired microcirculatory function. Additionally, as multiple organ involvement is associated with severe COVID-19 infection, endothelial cell infection has been a concern. Endotheliitis occurs due to viral involvement (as noted with presence of viral bodies) and the host inflammatory response.[21] Endotheliitis could explain the impaired microcirculatory function in different vascular beds (including the kidneys and lungs) and their clinical sequelae in patients with COVID-19. Thus, a therapy that targets the endothelial cells may play an important protective role in the treatment of this disease. This suggests that the E-selectin inhibitor, uproleselan (GMI-1271), may be a perfect agent to limit or eliminate the interactions between inflammatory cells, platelets and the endothelium, protect the lung and also decrease thrombosis.

E-selectin as a target for COVID-19

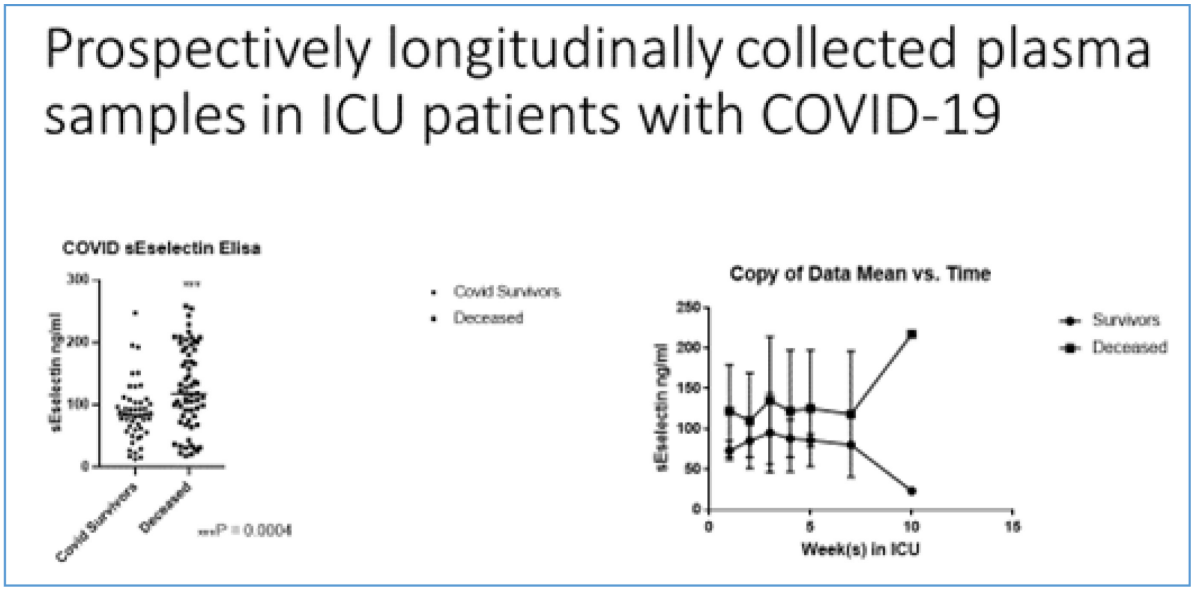
Soluble E-selectin is a significant biomarker for ARDS. Soluble E-selectin also has pro-inflammatory properties further releasing cytokines and promoting its synthesis and the continued influx of neutrophils. Blocking E-selectin with the weak natural carbohydrate ligands containing sialyl Le^x in an animal model of acute lung injury mitigated release of myeloperoxidase, permeability, and hemorrhaging. Small molecule glycomimetic antagonists of E-selectin (rivipansel and uproleselan) are 500- to 1000-fold more potent inhibitors of E-selectin and have shown activity and no measurable toxicity in human clinical trials for other indications. Treatment with these E-selectin inhibitors reduced the levels of soluble E-selectin in the bloodstream which occurs during recovery of ARDS. Thus antagonists of E-selectin which include glycomimetic antagonists and more specifically, rivipansel (GMI-1070) and uproleselan (GMI-1271), may be used to treat COVID-19 patients with respiratory symptoms that may lead to ARDS or who have already been diagnosed with ARDS.[22] Additionally, as endothelial cell infection and endotheliitis has been implicated as a cause of the multiple organ involvement associated with severe COVID-19, and that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and the host inflammatory response, a therapy that targets endothelial cells may play an important protective role in this disease.[21] In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19, and COVID-19 - endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds (including and importantly the kidneys) and their clinical sequelae in patients with COVID-19.

In addition to neutrophils as mentioned above, pathologic studies have also demonstrated a large number

of mononuclear cells in the lungs in non-survivors. So, what is the role of an E-selectin inhibitor in preventing the extravasation of monocytes into the tissues? It has been shown that GMI-1271 inhibits the influx of inflammatory cells: Monocytes (LY-6C^{hi}), Macrophages, Neutrophils and Myeloid cells into plaques,[23] inflammatory monocytes (LY-6C^{hi}) express PSGL-1 which is a risk factor for ARDS and these monocytes also bind the selectins,[24] and the influx of neutrophils is an earlier event that may usher in an influx of inflammatory monocytes (LY-6C^{hi}).[25] Thus, the timing of dosing with GMI-1271 should be most effective at an early time point, at the initial influx of neutrophils. E-selectin inhibition with GMI-1271 has been found to be effective in the inhibition of the same cytokines in an animal model of G-CSF induced sepsis that are released in the cytokine storm of severe COVID-19 patients.[12] Finally, a recent study from France has determined that sE-selectin is significantly increased in patients transferred into the ICU from the floor in COVID-19 patients admitted into the hospital. In this study, patients age 18 or greater with a positive SARS-CoV-2 test and an infectious syndrome were evaluated with values of 52,937 pg/ml in ICU patients (n20) and 37,931 in medicine patients not in the ICU (n20).[26] In a subsequent study of 32 patients with confirmed SARS-CoV-2 infection who underwent a whole blood gene expression profile analysis (11 ICU and 21 non-ICU cases), critically ill COVID-19 patients had a significant increased expression of E-selectin normalized RNA count.[26] Based on this data, an inhibitor to E-selectin should have efficacy in COVID-19.

We have measured soluble E-selectin levels in 12 patients who survived their COVID-19 infections vs. 12 patients who died from COVID-19 (many with multiple blood draws in each group). We found a statistically significant increase in levels of soluble E-selectin of those patients who died, as compared to those who survived.

We have also measured soluble E-selectin levels in our MM-ICU patients with COVID-19 pneumonia, respiratory failure and ARDS and determined that the levels are significantly increased, and that higher levels and increasing levels over time are associated with death (Figure below).



Summary of Published Background Supportive Data for the Treatment of COVID-19 with the E-selectin antagonist, Uproleselan

1. **E-selectin antagonist (Uproleselan; GMI-1271) inhibits thrombosis better than heparin and without a bleeding risk**
   Ref 1. Culmer DL et al (2017) Thromb. Haemost. 117: 1171-1181
   Ref 2. Myers D et al (2020) J. Vasc. Surg. 8(2): 268-278
   Ref 3. Devata S et al (2020) Res. Pract. Thromb. Haemost. 00: 1-2
2. **E-selectin is the first and critical step in the extravasation of inflammatory cells (monocytes and neutrophils) from the blood stream**
   Ref 4. Silva M et al (2018) Front. Immunology 8: 1-17
3. **E-selectin is the most significant biomarker for ARDS by both multivariate and univariate analysis.**
   Ref 5. Osaka D et al (2011) Int. J. Med. Sci. 8(4): 302-308
4. **PSGL-1 (an E-selectin ligand) is a risk factor for ARDS as determined by GWAS**
   Ref 6. Bime C et al (2018) Amer. J. Resp. Crit Care Med. 197(11): 1421-1432
5. **E-selectin natural ligand (sialyl Lex) inhibits acute lung injury in a mouse animal model**
   Ref 7. Mulligan MS et al (1993) J. Exp. Med. 179: 623-631
6. **Uproleselan (E-selectin antagonist) inhibits cytokine release**
   Ref. 8 Winkler IG et al (2018) Blood 131(1): 4552
7. **Uproleselan reduces E-selectin expression in patients in clinical trials and has a favorable safety profile**
   Ref. 9 DeAngelo DJ (2016) Blood 128(22): 4049

1.3 Study Agent(s) Background and Associated Known Toxicities

Selectins function in venous thrombosis presumably by binding and activating immune cells to initiate the coagulation cascade. E-selectin (CD62E) is known to bind and activate both monocytes and neutrophils. Uproleselan (GMI-1271) is a small molecule antagonist that specifically inhibits E-selectin and is rationally designed to mimic the bioactive conformation of the sialyl-Le^x carbohydrate ligand. E-selectin inhibition has been tested as a therapeutic for venous thrombosis. The pathophysiology of venous thrombosis has been driven by the concept of Virchow's triad: endothelial injury, circulatory stasis, and blood hypercoagulability. Inflammation was added when it was demonstrated that P-selectin, a glycoprotein, when inhibited decreased thrombosis in a primate AV fistula model. Early work suggested that both P-selectin and E-selectin were critical to the thrombotic process. E-selectin is also a key regulator of thrombus formation and fibrin content. In studies using GMI-1271 in a stasis mouse model of IVC thrombosis, the inhibitor was equivalent to LMWH for limiting thrombosis, but with a marked decrease in tail vein bleeding time.

Mice treated with GMI-1271 had decreased venous thrombus formation with significant inhibition at 10mg/kg BID (P=0.0271). Treatment with LMWH significantly decreased thrombus formation 2 days post induction at 6mg/kg (P=0.0203). All mice pre-treated prophylactically with GMI-1271 or LMWH followed the same pattern of decreasing thrombus weight 2 days post injury ($P<0.05$). In a second phase of this study, mice were administered a single bolus of saline (10 mg/kg), GMI-1271 (10mg/kg/day), or a therapeutic dose of LMWH (6 mg/kg/day) as predetermined by allometric scaling for mice to assess tail bleeding times. In the extended single dose monkey study where monkeys were dosed 250mg/kg and coagulation (PT and aPTT) was tested, no test article effects were seen. LMWH at 6mg/kg dose

significantly elevated tail bleeding times in mice versus controls (341±27, 491±60 vs. 82±6 seconds, P<0.01). GMI-1271 (10 mg/kg/day, IV) had significantly lower tail bleeding times compared to IV dose of LMWH (6mg/kg, p<0.01).

This and other data led to a clinical study (supported by NIH VITA) in which GMI-1271 was given to normal volunteers in a dose-dependent fashion as a one-time dose, then as a daily dose for 5 consecutive days compared to enoxaparin or saline, and finally to treat calf vein DVT.[27] There were no serious adverse events, GMI-1271 did not affect thromboelastographic parameters, lower levels of sE-sel were found in GMI-1271 treated subjects (as expected for on-target effects), and there was lower leukocyte and platelet activation in GMI-1271 treated volunteers (determined by MPO and MAC-1 levels). Two patients with calf vein DVT were treated with GMI-1271 with a 5-day intravenous course. Both patients had immediate relief of pain and significant increase in vein recanalization by day 19. The effectiveness of GMI-1271 has been confirmed in a primate model of proximal iliac vein thrombosis, both inhibiting thrombosis and vein wall fibrosis (supported by NIH VITA).[28, 29] In fact, GMI-1271 was more effective in inhibiting thrombosis and protecting again vein wall fibrosis than a combination of GMI-1271 plus LMWH.[29] This strongly suggests that E-selectin has a significant role in both thrombogenesis and post-thrombotic syndrome after DVT and may be an excellent pharmacologic target.

In a recent publication,[12] Carl June and John Moore report that severe disease leading to ARDS has been described in up to 20% in COVID-19 cases. They further state that the pathology of disease is similar to cytokine-release syndrome (CRS)-induced ARDS observed in leukemia patients undergoing CAR-T cell therapy. CRS was also found to be the major cause of morbidity in patients infected with other coronaviruses such as SARS-CoV and MERS-CoV. The cytokine storm in these diseases consisted of the release of inflammatory cytokines such as IL1β, IL-8, IL-23 as well as IL-6.[13] Monocytes and macrophages are targeted by SARS-CoV-2 by binding to cell surface ACE2 receptors. These cells are also known to contribute to the development of CRS that is observed in patients receiving CAR-T cell therapy. To target these cells, GM-CSF was inhibited by genetic ablation of CAR T-cells (GM-CSFk/o CAR-T cells) (ref. 8) which effectively reduced CRS and enhanced therapy. To simulate the effects of GM-CSF inducing cytokine release in patients, mice were dosed with G-CSF and inflammatory cytokines were measured in fluids derived from a femoral flush. Treatment of mice with uproleselan significantly inhibited expression of cytokines that are found in COVID-19 patients experiencing cytokine release syndrome (CRS).

Uproleselan has been studied extensively in toxicology studies, including in multiple species (rodent and non-rodent). In 91-day repeat-dose studies in mice and monkeys, the no observed effect levels (NOEL) was the highest doses tested, 2000 mg/kg/day in mice and 500 mg/kg/day in monkeys. No test article related effects were found in the following parameters and endpoints in both species: mortality, clinical signs, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis, gross necropsy findings, organ weights, or histopathologic examinations. In addition, there were no findings after electrocardiographic examinations in monkey. Safety pharmacology testing suggests no cardiovascular, respiratory, or

central nervous system (CNS) risk to humans. Uproleselan has no known mutagenic potential. Therefore, continuing human studies are supported by the existing toxicology, safety pharmacology and genotoxicity data. For additional information, refer to the IB.

This study will be conducted under the US IND #155100. Comprehensive preclinical testing has been completed in advance of human clinical trials. Full details of the preclinical program can be found in the uproleselan Investigator's Brochure (IB).

The doses of uproleselan have been determined using pre-clinical data. The therapeutic range of uproleselan is believed to lie between 2 to 40 mg/kg (see uproleselan Investigator's Brochure). Uproleselan is an IV formulation that has been extensively tested in humans by GMI in several studies in healthy volunteers, patients with calf level DVT, and patients with acute myeloid leukemia (AML) and multiple myeloma (MM).

Uproleselan (GMI-1271) is an E-selectin antagonist. Soluble E-selectin (sE-selectin) is a significant biomarker for ARDS and has recently been described as biomarker for progression of disease in COVID-19 patients (1). In a recovering COVID-19 patient the concentration of sE-selectin in the blood correlates with improvement and with other markers of COVID-19 infection (IL-6, ferritin and ACE2) as shown in **Figure**.

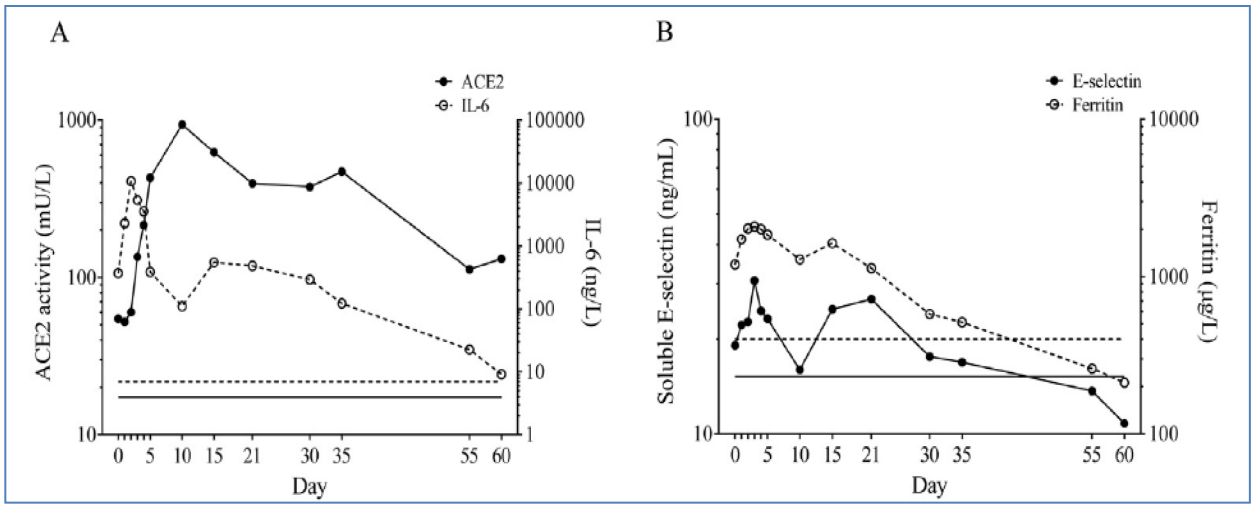


Figure. sE-selectin correlation with clinical outcome and other biomarkers in a COVID-19 patient (ref.1)

Soluble E-selectin also has pro-inflammatory properties further releasing cytokines and promoting its synthesis and the continued influx of neutrophils. Blocking E-selectin with the weak natural carbohydrate ligands containing sialyl Le^x in an animal model of acute lung injury mitigated release of myeloperoxidase, permeability and hemorrhaging. Small molecule glycomimetic antagonists of E-selectin (Rivipansel and Uproleselan) are 500- to 1000-fold more potent inhibitors of E-selectin and have shown activity and no measurable toxicity in human clinical trials for other indications.

Treatment with these E-selectin inhibitors reduced the levels of soluble E-selectin (sE-selectin) in the bloodstream of patients in these 2 different clinical trials. A dose of 10mg/ml was chosen based on scaled

doses from efficacy animal models of AML and blood levels corresponding to IC_{90} values of uproleselan for E-selectin determined in assays. The effects of dosing uproleselan (10mg/kg) with treatment of AML patients on circulating sE-selectin levels is shown in **Figure** below - there is a significant drop in soluble E-selectin levels over time, up to 200 hours.

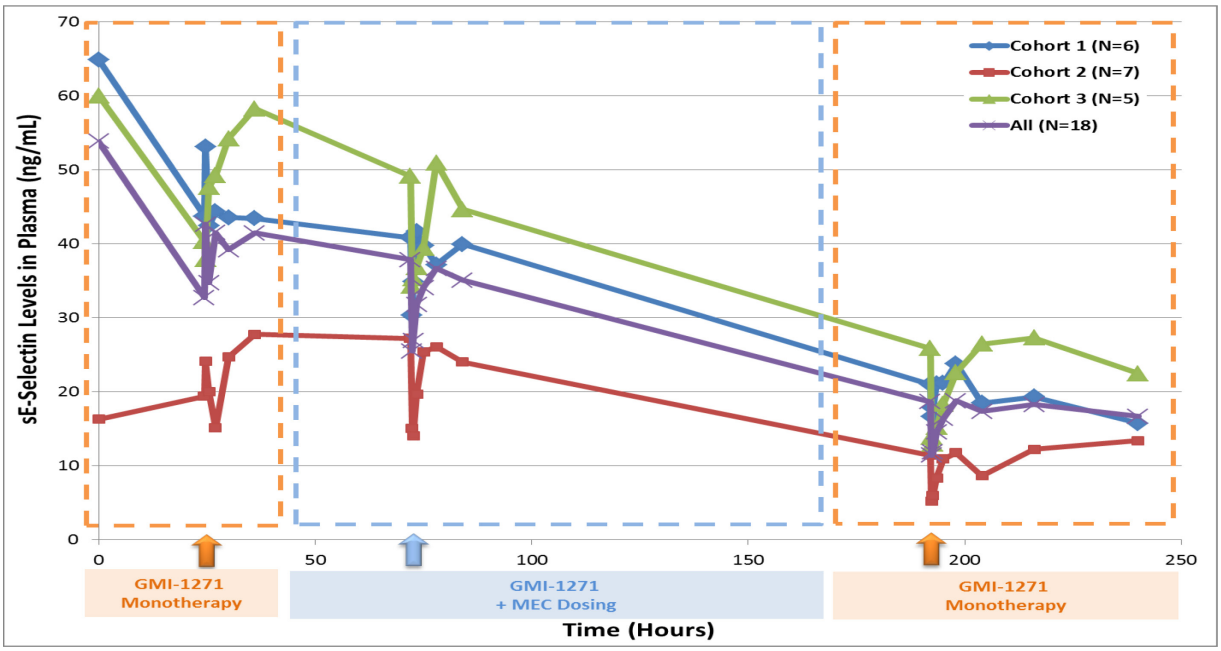


Figure. Uproleselan decreases blood concentrations of sEselectin in AML patients.
Nagy B. Jr. et.al. A dramatic rise in serum ACE2 activity in a critically ill COVID-19 patient. Int. J. Inf. Disease 103: 412-414 (2021)

In our clinical study performed in normal volunteers and in patients with calf vein DVT, we found levels of soluble E-selectin to be a good marker for on-target effects of GMI-1271, and lower levels of soluble E-selectin were found in daily GMI-1271-treated volunteers after 4 days.[27] Thus, we wish to follow the decrease in soluble E-selectin levels as a means to determine the efficacy of uproleselan treatment. In a recent publication, reduction of soluble E-selectin in COVID-19 patients correlated with improved prognosis. Soluble E-selectin was found to be a marker for severity in COVID-19 patients and predicts those who will need to go to the ICU for more intensive care as opposed to those who did not progress to ICU-level care. [44] Thus, the antagonist of E-selectin, uproleselan (GMI-1271), may be used to treat COVID-19 patients with respiratory symptoms that may lead to ARDS or who have already been diagnosed with ARDS. Additionally, as endothelial cell infection and endotheliitis have been implicated as a cause of the multiple organ involvement associated with severe COVID-19, and that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and the host inflammatory response, a therapy that targets endothelial cells may play an important protective role in this disease. These data strongly suggest that E-selectin may be an excellent pharmacologic target to reduce progression to ARDS in patients with acute COVID-19 pneumonia.

Given the severe acute nature of COVID-19 and the clear relationship of patient outcome to soluble E-

selectin levels, a dose at the higher end of 40 mg/kg range of doses evaluated in healthy volunteers was desired to exert a strong pharmacological effect with minimal safety risk for this acute severe inflammatory event. In addition to the precedented exposure in healthy volunteers, the 20 mg/kg dose selected for this trial is equivalent to the highest dose tested in AML patients in study GMI-1271-201. Thus, this dose level has precedent in both healthy volunteers and patients with advanced cancer.

In addition to human exposure, uproleselan has been extensively studied in non-clinical toxicology studies, including 91-day repeat dose studies. The NOEL from 91-day repeat dose studies in mice and cynomolgus monkeys is 2000 mg/kg and 500 mg/kg, respectively. These non-clinical dose levels provide a 5-fold mean safety margin compared the exposure expected from a 20 mg/kg human dose.

Furthermore, exposure response analyses demonstrated that safety and efficacy responses are not dependent on exposure over the range of exposures attained in the GMI-1271-201 trial, which administered dose levels of 5, 10 and 20 mg/kg Q12h. Pharmacokinetic analysis of study GMI-1271-201 revealed dose related increases in exposure and, importantly, dose related increases in the time above IC_{50} and IC_{90} for E-selectin.

The 20 mg/kg dose level selected for this trial provides COVID-19 patients optimal exposures to maximize the time that uproleselan remains above the E-selectin inhibitory concentration level and the potential pharmacologic response while remaining within the range of doses already evaluated in humans.

In summary, a 20 mg/kg dose for the COVID-19 trial was selected in order to provide a safe dose, within the range of doses already evaluated in humans, and to provide uproleselan exposures sufficient to ensure a pharmacologic effect in a single arm trial.

To date, 189 subjects who have received uproleselan are included in the integrated safety analyses (86 healthy volunteers and 103 subjects with AML, MM, or DVT).
The majority of subjects (114/189) have received uproleselan 10 mg/kg. A total of 86 subjects received at least 1 dose of uproleselan in the healthy volunteer studies.
Ten subjects received 2 mg/kg uproleselan, 22 received 5 mg/kg, 32 received 10 mg/kg, 13 received 20 mg/kg, 4 received 40 mg/kg, and 5 subjects received 800 mg uproleselan.
Refer to uproleselan Investigator's Brochure for a summary of TEAEs with incidence ≥10% (very common) reported for all treated subjects in the healthy volunteer studies of uproleselan. Overall, 49 subjects (49/86, 57.0%) experienced at least 1 TEAE. Incidence rates were similar among dose groups.

TEAEs were most frequently reported in the System Organ Classes (SOCs) of nervous system disorders (23/86 subjects, 26.7%), musculoskeletal and connective tissue disorders (17/86,19.8%), and general disorders and administration site conditions (16/86 subjects, 18.6%). Overall, the most frequently reported TEAEs were headache (19/86 subjects, 22.1%), back pain (15/86, 17.4%), and infusion site pain (9/86 subjects, 10.5%). No nonserious TEAEs with a severity Grade ≥3 were

reported in any of these healthy volunteer trials.

In studies of uproleselan in subjects with AML, MM, and DVT, 103 subjects received uproleselan and are included in the safety analyses (91 in the AML study, 10 in the MM study, and 2 in the DVT study). The majority of subjects received uproleselan 10 mg/kg (82/103), while 13/103 received 5 mg/kg uproleselan and 8/103 received 20 mg/kg uproleselan. Refer to uproleselan Investigator's Brochure for a summary of TEAEs with incidence ≥10% (very common) reported for all treated subjects in these studies.
Overall, 100 subjects (100/103, 97.1%) experienced at least 1 TEAE. Incidence rates were similar among dose groups. TEAEs were most frequently reported in the SOCs of gastrointestinal disorders (91/103 subjects, 88.3%), general disorders and administration site conditions (82/103, 79.6%), blood and lymphatic system disorders (77/103, 74.8%), metabolism and nutrition disorders (71/103, 68.9%), and respiratory, thoracic and mediastinal disorders (57/103 subjects, 55.3%).

Overall, the most frequently reported TEAEs for subjects who have received uproleselan (101 of whom received uproleselan in addition to their chemotherapy regimens) were diarrhea (69/103 subjects, 67.0%), febrile neutropenia (60/103, 58.3%), nausea (59/103, 57.3%), fatigue (47/103, 45.6%), decreased appetite (40/103, 38.8%), constipation (36/103, 35.0%), hypokalemia (36/103, 35.0%), edema peripheral (35/103, 34.0%), chills (33/103, 32.0%), and vomiting (32/103 subjects, 31.1%).

Refer to uproleselan Investigator's Brochure for a summary of treatment-emergent SAEs for all 189 subjects who have received uproleselan (101 of whom received uproleselan in addition to their chemotherapy regimens) in clinical trials. To date, 36 subjects have experienced at least 1 SAE (36/189 subjects, 19.0%). Eight of 35 subjects (8/35, 22.9%) who received 5 mg/kg uproleselan, 25/114 subjects (21.9%) who received 10 mg/kg uproleselan, and 3/21 subjects (14.3%) who received 20 mg/kg uproleselan experienced at least 1 SAE during their participation in clinical studies. No SAEs have occurred in the 19 subjects dosed with 2 mg/kg, 40 mg/kg, or 800 mg uproleselan.

Across all studies, the only SAEs reported for >2% of subjects were febrile neutropenia (7/189 subjects, 3.7%), sepsis (5/189, 2.6%), and pneumonia (4/189 subjects, 2.1%). Only 1 SAE was reported in the healthy volunteer studies (unrelated Grade 2 muscular weakness). (Refer to the uproleselan IB for further information).

1.4 Rationale/ Novelty

Uproleselan is an E-selectin antagonist. Soluble E-selectin is a significant biomarker for ARDS. Soluble E-selectin also has pro-inflammatory properties further releasing cytokines and promoting its synthesis and the continued influx of neutrophils. Blocking E-selectin with the weak natural carbohydrate ligands containing sialyl Le^x in an animal model of acute lung injury mitigated release of myeloperoxidase, permeability, and hemorrhaging. Small molecule glycomimetic antagonists of E-

selectin (Rivipansel and Uproleselan) are 500- to 1000-fold more potent inhibitors of E-selectin and have shown activity and no measurable toxicity in human clinical trials for other indications. Treatment with these E-selectin inhibitors reduced the levels of soluble E-selectin in the bloodstream which occurs during recovery of ARDS. Thus antagonist of E-selectin Uproleselan (GMI-1271) may be used to treat COVID-19 patients with respiratory symptoms that may lead to ARDS or who have already been diagnosed with ARDS.[22] Additionally, endothelial cell infection and endotheliitis have been implicated as a cause of the multiple organ involvement associated with severe COVID-19 and SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and the host inflammatory response. Therefore, a therapy that targets endothelial cells may play an important protective role in this disease.[21] This strongly suggests that E-selectin may be an excellent pharmacologic target to reduce progression to ARDS in patients with acute COVID-19 pneumonia.

Endothelial injury is an underlying mechanism that links inflammation and thrombosis in severe COVID-19. The combination of elevated selectin levels, high VWF levels, microvascular thrombosis, and microvascular inflammation all suggest that microvascular injury may be a common trigger for both the inflammatory and thrombotic complications of COVID-19. E-selectin levels were significantly increased in COVID-19 patients requiring hospitalization from ED (pdf attached). Inhibitors of endothelial exocytosis may represent a novel therapeutic approach to the vasculopathy of COVID-19. Inhibition of selectin would block part of the pathway downstream of endothelial injury, including leukocyte rolling and platelet adherence to the vessel wall. We have also measured soluble E-selectin levels in our MM-ICU patients with COVID-19 pneumonia, respiratory failure and ARDS and determined that the levels are significantly increased, and that higher levels and increasing levels over time are associated with death (Figure above).

1.5 Correlative Studies/Special Studies

Biomarkers to evaluate the effects of Uproleselan

The measurement of biomarkers of coagulation, inflammation and angiogenesis in subjects exposed to uproleselan vs. standard of care will enable us to evaluate the effect of Uproleselan on the progression of acute respiratory failure in patients with severe COVID-19 pneumonia. The biomarkers chosen will be indicators of disease severity and progression as well as drug efficacy.

Currently there is no single biomarker that can specifically detect venous thrombosis or its associated inflammatory response in patients. Ramacciotti et al have demonstrated the usefulness of combining circulating biomarkers of coagulation and inflammation to determine a clinical profile that can exclude or confirm if a patient has DVT.[30] Therefore in this application we will determine if the previously measured biomarkers which include **D-dimer** as a measure of clot production and breakdown and are significantly elevated in COVID-19 infection and correlate with disease severity;[31-33] **soluble E-selectin (**E-selectin specifically shown to have highly elevated levels in COVID-19 positive patients transferred into the ICU)[26] and **soluble P-selectin**, which are essential glycoproteins expressed during clot formation; **Interleukin-6 (IL-6)** and **interleukin-10 (IL-10)** which are cytokines involved with systemic inflammation that rise with

venous thrombosis and potential players in the cytokine storm phenomenon at play in COVID-19 patients experiencing ARDS. The 4-day change in IL-6:IL-10 ratio, chosen to derive the Dublin-Boston score, was associated with more severe outcomes with COVID-19;[34] **Angiopoietin-2**, an angiogenic growth factor affecting cardiovascular remodeling and indicator of endothelial cell activation shown to be predictive of severe COVID-19 infection,[26, 35] and **TNF-alpha** an acute phase proinflammatory cytokine which may be another indicator of disease severity during COVID-19 infection.[36]

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine the safety of uproleselan in patients with severe COVID-19 pneumonia.

2.2 Secondary Objectives

To evaluate if treatment with uproleselan administered intravenously in addition to the best available therapy according to institutional guidelines is able to reduce the progression of acute respiratory failure, in patients with severe COVID-19 pneumonia.

- To evaluate overall survival and all-cause mortality at day 15 and 28.
- To evaluate changes in the COVID ordinal outcomes scale.
- To assess adverse events to evaluate the safety of uproleselan.
- To assess ventilator-free days, ICU-free days, oxygen, vasopressor free days.
- To evaluate changes in D-dimer.

Exploratory Objectives:

- To examine the correlation of plasma soluble E-selectin concentrations with clinical outcomes.
- To examine the correlations of other biomarkers of interest with clinical outcome.

3. ENDPOINTS

3.1 Primary Endpoints: Safety of uproleselan in patients with severe COVID-19 pneumonia.

3.2 Secondary Endpoints

- Reduction in the progression to acute respiratory failure [Time Frame: 15 days for primary endpoint].
- Patients with a baseline PaO2/FiO2 >= 200: progression of respiratory failure is defined by:
  a. severe gas transfer deficit (PaO2/FiO2 < 200);
  b. persistent respiratory distress while receiving oxygen (persistent marked dyspnea, use of accessory respiratory muscles, paradoxical respiratory movements);
- The rate will be calculated as the proportion of patients who experienced at least one of the events above by day+15 from treatment start.

- Reduction in the progression to acute respiratory failure [Time Frame: 28 days].
- Overall survival and all-cause mortality (day 15, day 28).
- Time to improvement in oxygenation for at least 48 hours. Improvement in oxygenation is defined as an increase in PaO2/FiO2 of 50 (or greater) compared to the nadir of PaO2/FiO2.
- Number of patients requiring mechanical ventilation, if not on mechanical ventilation at study entry.
- Change in the WHO COVID-19, "8-point ordinal scale" from study entry to day 28 (Table 1). To be assessed on day 3, day 8, day 15, day 28.
- Duration of hospitalization and duration of ICU care.
- Toxicity assessment (including incidence of grade 3-5 hemorrhagic events).
- Change in D-dimer [Time Frame: baseline, study day 3, day 8, day 15, and day 28]. Changes in plasma D-dimer level compared with baseline at enrollment.
- Decrease or Change in IL-6:IL-10 ratios.
- Free-Days- at day 28
    - Oxygen
    - Ventilator
    - Vasopressor
    - ICU
    - Hospitalization

Table 1: WHO Ordinal Scale Ordinal Score

Patient State	Descriptor	Score
Ambulatory	No limitation of activities	1
	Limitations of activities	2
Hospitalized (mild disease)	No oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized (severe disease)	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Mechanical ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Exploratory Endpoints

- Soluble E-selectin and P-selectin levels compared with baseline at enrollment.
- Thrombosis free days (clinically defined) at day 28.
- Change in other cytokine levels, endothelial or leukocyte activation (day 1, 15, 28) in IL-6, IL-10, Angiopoietin-2, and TNF-alpha

4. SUBJECT ELIGIBILITY

Patients with confirmed severe COVID-19 pneumonia admitted to hospital, requiring supplemental oxygen. Subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the study. Study treatment may not begin until a subject is enrolled.

4.1 Inclusion Criteria

1. Adults, ages 18-85 years.
2. Willing and able to provide informed consent prior to performing study procedures unless they have a legally authorized representative (LAR).
3. Documented COVID-19 pneumonia: defined as upper respiratory tract specimen (nasopharyngeal swab (NPS) or viral throat swab) positive for COVID-19 and/or imaging at computed tomography scan suggestive of COVID-19 pneumonia.
4. Confirmed coronavirus (SARS-CoV-2) infection admitted to the hospital, enrolled ≤ 48 hours of need for supplemental oxygen.
5. Currently hospitalized requiring supplemental oxygen.
6. Have severe COVID-19 according to the WHO Interim Guidance with confirmation by real-time RT-PCR assay. The enrollment criteria with one of the following: respiratory distress, RR ≥30 beats/min; oxygen saturation level less than 93% in resting state; or partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg.
   WHO, Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: Interim guidance. https://www. who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infectionwhen-novel-coronavirus-(ncov)-infection-is-suspected.
7. Willing and able to participate in all required evaluations and procedures.

4.2 Exclusion Criteria

1. In the opinion of at least one investigator, unlikely to survive for >48 hours from screening.
2. Severe chronic respiratory disease (e.g. COPD or other) requiring supplemental oxygen and/or having required mechanical ventilation pre-COVID-19 infection.
3. Concurrent enrollment in a COVID related interventional drug trial. Use of remdesivir, steroids, and convalescent plasma are permitted along with other standard of care therapies for COVID.[37]
4. Currently on invasive mechanical ventilation.
5. Hypotension defined as systolic blood pressure < 90 mmHg on two sequential readings at least 4 hours apart.
6. Total Bilirubin ≥ 3 x upper limit of normal (ULN), Creatinine Clearance ≤ 30 mL/min/1.73m^2.
7. Pregnant or breastfeeding.
8. Known diagnosis of an acute thrombosis on admission.
9. Concurrent dual antithrombotic therapy (aspirin or P2Y12 inhibitor plus anticoagulation to treat deep venous thrombosis or pulmonary embolism (single antiplatelet or anticoagulant agent at prophylactic dose is permitted).
10. Concomitant use of thrombolytic therapy.
11. Concomitant therapeutic systemic anticoagulant therapy (e.g. heparin, warfarin, direct thrombin inhibitors and direct factor Xa inhibitors). As per NIH Guidelines: Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults (AIII). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII); https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/
12. History of recent major bleeding, defined in accordance with the criteria of the International Society on Thrombosis and Hemostasis (ISTH).
13. History of bleeding disorder thought to impose excessive bleeding risk as per investigator discretion
14. Hemodynamic instability, defined as inability to maintain mean arterial pressure.
15. Hypersensitivity to the active substance or to any of the excipients of uproleselan.
16. Any physical examination findings and/or history of any illness that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study

5. SUBJECT SCREENING AND ENROLLMENT PROCEDURES

Patients who present to the University of Michigan Health System who have **confirmed severe COVID-19 pneumonia admitted to hospital, requiring supplemental oxygen** will be recruited. The study research team will contact the potential subject to discuss the study in detail and review the informed consent document. Prior to any study-specific screening evaluations and clinical trial participation, written informed consent will be obtained from each potential subject or legally authorized representative (LAR) in the clinical trial using the Institutional Review Board (IRB) approved informed consent form (ICF). Potential subjects will be informed in detail about the study products to be administered, and the nature of the clinical investigation. The subjects will also be informed that they are free to withdraw their consent and discontinue their participation in the clinical trial at any time. Each subject will be given a copy of the signed ICF.

5.1 Treatment Dosage and Administration

Protocol treatment must start within 48 hours of the admitted patient requiring supplemental oxygen for documented COVID-19 pneumonia. Study enrollment is defined as the day subject meets all of the inclusion criteria and none of the exclusion criteria.

5.1.1 Treatment Plan

Up to 15 subjects will be enrolled in this prospective, interventional, single-arm, open label trial.
All drug administration will be performed by nurses in the inpatient unit. Uproleselan injection is a sterile solution for IV administration, supplied in single-dose vials at a concentration of 50 mg/mL. Uproleselan should be administered intravenously (IV) into a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC). Infusion should take place at a steady rate over a period of 20 minutes ±2 minutes using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration is highly recommended. Dilution of uproleselan may be performed with normal saline (0.9% Sodium Chloride) up to 5x as needed for ease of administration and per institutional practice. Compatibility with other therapeutic agents has not been determined, therefore uproleselan should not be administered concurrently with anything other than saline. When flush is used, saline flush is preferred.

Table 2: Description of Treatment

Agent	Premedications/ Precautions	Dose	Route	Schedule
Uproleselan (GMI-1271)	None	20 mg/kg BID, up to a maximum dose of 2500 mg	IV infusion over 20 min	Daily on treatment days 1-7

Table 3: Standard of Care Treatments

1. Supplemental oxygen, escalate to heated high flow nasal cannula, noninvasive ventilation, endotracheal intubation and mechanical ventilation as needed.
2. Conservative fluid management strategy.
3. Dexamethasone 6mg (PO or IV) qD for up to 10d (RECOVERY trial, Horby PW et al.[38]
4. Remdesivir 200 mg loading dose, then100 mg daily for up to 9 additional days (ACTT-1 Study, Beigel JH et al.).[39]
5. Convalescent plasma for compassionate use.
6. Other medical management as recommended by Infectious Disease Consultants.
7. Management of septic shock.
8. ICU admission as required.

5.2 Assessment for Toxicities

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of toxicity according to the Time and Events Table (Table 3). Toxicity will be assessed according to the CTCAE v. 5.

All drug administration will be performed by nurses in the inpatient unit. Routine vital sign measurement will be performed and all adverse events (AEs) will be recorded. Toxicities will be classified as AEs probable, possible, unlikely or unrelated to uproleselan.

5.2.1

Evaluating for progression to Acute Respiratory Failure

- Reduction in the progression to acute respiratory failure [Time Frame: 15 days].
- Patients with a baseline PaO2/FiO2 >= 200: progression of respiratory failure is defined by:
  a. severe gas transfer deficit (PaO2/FiO2 < 200).
  b. persistent respiratory distress while receiving oxygen (persistent marked dyspnea, use of accessory respiratory muscles, paradoxical respiratory movements).
- The rate will be calculated as the proportion of patients who experienced at least one of the events above by day+15 from treatment start.
- Overall survival and all-cause mortality (day 15, day 28).
- Time to improvement in oxygenation for at least 48 hours. Improvement in oxygenation is defined as an increase in PaO2/FiO2 of 50 (or greater) compared to the nadir of PaO2/FiO2.
- Number of patients requiring mechanical ventilation, if not on mechanical ventilation at study entry.
- Change in the WHO COVID-19, “8-point ordinal scale” from study entry to day 28 (Table 1). To be assessed on day 3, day 8, day 15, day 28.
- Duration of hospitalization and duration of ICU care.
- Toxicity assessment (including incidence of grade 3-5 hemorrhagic events).
- Change in D-dimer [Time Frame: baseline, study day 3, day 8, day 15, and day 28]. Changes in plasma D-dimer level compared with baseline at enrollment.
- Decrease or Change in IL-6:IL-10 ratios.

- Free-Days- at day 28
  - Oxygen
  - Ventilator
  - Vasopressor
  - ICU
  - Hospitalization

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Hospitalized (mild disease)	No oxygen therapy	3
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Hospitalized (severe disease)	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Mechanical ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Exploratory Endpoints

- Soluble E-selectin and P-selectin levels compared with baseline at enrollment.
- Thrombosis free days (clinically defined) at day 28.
- Change in other cytokine levels, endothelial or leukocyte activation (day 1, 15, 28) in IL-6, IL-10, TNF-alpha and Angiopoietin-2.

5.3 Concomitant Medications/Treatments

Table 3: Standard of Care Treatments[40]

1. Supplemental oxygen, escalate to heated high flow nasal cannula, noninvasive ventilation, endotracheal intubation and mechanical ventilation as needed.
2. Conservative fluid management strategy.
3. Dexamethasone 6mg (PO or IV) qD for up to 10d (RECOVERY trial, Horby PW et al. [38]
4. Remdesivir 200 mg loading dose, then100 mg daily for up to 9 additional days (ACTT-1 Study, Beigel JH et al. [39]
5. Convalescent plasma for compassionate use.
6. Other medical management as recommended by Infectious Disease Consultants.
7. Management of septic shock.
8. ICU admission as required.

5.4 Duration of Therapy

Each subject in the treatment arm will receive one dose of uproleselan every 12 hours (12 hours apart optimally; acceptable range 10-14 hours) on treatment days 1-7.

5.5 Duration of Follow-Up

Subjects will be followed for 28 days. Subjects with treatment-emergent adverse events will be followed until resolution or stabilization of the adverse event.

5.6 Off Study Criteria

Subjects can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. If possible, subject will follow protocol procedures related to safety analysis. The reason(s) for discontinuation from study will be documented and may include:

- Subject withdraws consent (termination of treatment and follow-up).
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment and follow-up.
- Subject is unable to comply with protocol requirements.
- Treating physician judges continuation on the study would not be in the subject's best interest.
- Drug-related toxicity or adverse event, which contraindicates continuation in the study
- Subject becomes pregnant: If patient pregnancy results become known during treatment period, pregnancy should be followed and specific monitoring as per NIH guidelines conducted.[41]
- Termination of the study by The University of Michigan or GlycoMimetics Inc.
- Subject completes protocol treatment and follow-up criteria.

5.7 Subject Replacement

Subjects will be replaced in this study if they are removed.

6 STUDY PROCEDURES

6.1 Screening Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Hematology, serum chemistry or coagulation assessments performed for clinical indications will be used from hospital admission. All screening procedures, unless noted above, must be performed within 48 hours of subject's requirement of supplemental oxygen for diagnosis of COVID pneumonia and prior to enrollment unless otherwise stated. The screening procedures include:

- Informed Consent
- Demographics
- Age, gender, race, ethnicity
- Complete medical and surgical history
- Review subject eligibility criteria
- Review and record prior and concomitant medications/therapies
- Physical exam including vital signs, height and weight

Vital signs include temperature, pulse, respirations, blood pressure
- Hematology, serum chemistry and coagulation studies
- Serum pregnancy test (for females of child-bearing potential)

6.1.1 Procedures during Study Drug Treatment Visits

If a laboratory parameter has been obtained within 48 hours prior to study enrollment, it does not need to be repeated for study purposes and will be considered the *baseline* value. Following the last day of study, no further "study related" blood tests will be obtained.

Guidelines for monitoring hematologic and coagulation parameters were derived from Thachil, J., et al., *ISTH interim guidance on recognition and management of coagulopathy in COVID-19.* J Thromb Haemost, 2020. **18**(5): p. 1023-1026.[42]

- **Pulmonary Indices**: Pulmonary parameters will be recorded daily for subjects from the time of study entry to cessation of study drug therapy. Pulmonary assessment will include a subject's current level of supplemental oxygen support (%FiO2), current modality of support (mechanical ventilation, BiPaP, CPAP, nasal cannula, or none), and the results of any chest radiographs (if performed) that day. For patients that remain hospitalized on day 15 or 28 of study, pulmonary indices will also be made at that time point. Blood gas values will be obtained as clinically indicated. Scoring from the WHO COVID Ordinal Scale (Table 1) will be determined as indicated by study investigators or study coordinators.

- **Hematologic parameters:**
  A complete blood count including platelets (CBCP) should be obtained at baseline (study entry), and daily until cessation of study therapy. Additional blood counts may be obtained as clinically indicated.

- **Chemistries:**
  Serum chemistries (Electrolytes, BUN, creatinine, liver panel) should be obtained at baseline (study entry), and daily until cessation of study therapy. Additional chemistries should be obtained as clinically indicated.

- **Coagulation Labs:**
  D-dimer, Prothrombin time (PT), activated partial thromboplastin time (aPTT), and serum fibrinogen should be obtained at baseline (study entry). Additional D-dimer, PT, and serum fibrinogen testing may be obtained as clinically indicated.

- **Serologic Cytokine Profiles:** Biomarkers will be drawn on day 0-1 pre-study drug administration, days 1-7, day 15, and day 28. These will be used to measure e-selectin levels and are not for safety labs. Due to current hospital understaffing, blood draws will occur as staffing permits. Missed blood draws will not be counted as protocol deviations.

6.2 Study Schedule of Events

Table 4: Events of the Study

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 15	Day 28
Eligibility screen	X										
Informed Consent	X										
Medical history	X										
Physical Exam	X	X	X	X	X	X	X	X			
CBC	X[a]	X	X	X	X	X	X	X			
Chemistries	X[a]	X	X	X	X	X	X	X			
ABG	X[a]										
CXR	X[b]										
Biomarkers [g]	X	X	X	X	X	X	X	X		X	X
D-dimer [g]	X			X					X	X	X
Serum pregnancy test	X[c]										
Pulmonary indices[d]	X	X	X	X	X	X	X	X	X	X	X
Uproleselan		X	X	X	X	X	X	X			
Vital Signs[e]		X	X	X	X	X	X	X			
COVID scale	X			X					X	X	X
AE and follow-up[f]		X	X	X	X	X	X	X	X	X	X

Key: CBC-complete blood count; CXR-chest X ray; ABG-arterial blood gas; BP-blood pressure; HR-heart rate; RR-respiratory rate.

Notes:

a. Laboratory tests performed within 48 hours prior to study enrollment do not need to be repeated at baseline. CBC should be performed daily (until cessation of study therapy) and should be viewed as standard medical care. Arterial blood gas (ABG) measurements, and chest radiographs should be performed per routine medical care. Venous blood gas may be used when ABG unavailable. Patients should continue to have laboratory tests performed (as indicated above) until cessation of study therapy.

b. Chest X-Ray (CXR): The CXR does not need to be repeated at baseline, if a CXR was done on admission and revealed bilateral infiltrates.

c. Pregnancy test: Perform in subjects of child-bearing potential, if not already performed this admission for clinical care reasons.

d. Pulmonary indices will be recorded daily until cessation of drug therapy, and again at day 8, 15 and 28 (if a patient remains hospitalized at that time). Patients who are discharged prior to day 15 or 28 do not need to have pulmonary indices assessed on day 15 or 28.

e. Vital signs: heart rate, respiratory rate, blood pressure prior to and upon completion of each infusion.

f. Adverse Event Reporting and Follow-up: Patients will be assessed for adverse events daily during receipt of study therapy, and for 7 days following completion of study drug therapy, provided they remain hospitalized during this 7-day post-therapy period. In addition, patients will be contacted on day 15 and 28 (±2 days), to assess their clinical status and any active adverse events at that time. This final assessment can be done virtually, by telephone or electronically (email) if the patient cannot be contacted by phone. No in-person visit is required.

g. Study blood draws, including D-dimer and biomarkers, will only occur if patient is still hospitalized and as hospital staffing permits (weekends/holidays may not be feasible). No outpatient study blood draws will be performed.

Table 5: Parameters to be Tested for Hematology, Serum Chemistry, and Coagulation Studies

Category	Parameters
Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, mean platelet volume, red blood cells (RBCs), white blood cells (WBCs) with complete differential including neutrophils, lymphocytes, monocytes, basophils, eosinophils, immature granulocytes
Serum chemistry	Comprehensive metabolic panel (CMP) to include: total protein, albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, BUN, creatinine, estimated glomerular filtration rate (EGFR) (ml/min), electrolytes (sodium, potassium, calcium, chloride, bicarbonate), and glucose
Coagulation	Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen

7 MEASUREMENT OF EFFECT

7.1 Safety/Tolerability

AE assessment will be performed for all subjects. The study will use the Common Terminology Criteria for Adverse Events (CTCAE) 5. Physical examination, vital signs, laboratory tests will be performed. Vitals will be taken 10-30 minutes before/after infusion OR at the closest time points possible if not possible in the 10-30 minute period.

7.2 Efficacy

Reduction in the progression to acute respiratory failure [Time Frame: 15 days]

Patients with a baseline PaO2/FiO2 >= 200: progression of respiratory failure is defined by:
a. severe gas transfer deficit (PaO2/FiO2 < 200)

b. persistent respiratory distress while receiving oxygen (persistent marked dyspnea, use of accessory respiratory muscles, paradoxical respiratory movements)

The rate will be calculated as the proportion of patients who experienced at least one of the events above by day+15 from treatment start.

8 ADVERSE EVENTS

8.1 Experimental Therapy

For the most recent safety update, please refer to the current uproleselan IB.

Contraindications:

- Hypersensitivity to uproleselan or related products
- Interaction with other medications
- Adverse Reactions

Please refer to Section 6.2 for details; these will be reported during the study.

8.2 Definitions

8.2.1 Adverse Event Reporting Requirements

Purpose: Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

Adverse Event Reporting:
The descriptions and grading scales used in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE v5.0 mapping document can be downloaded at the CTEP website: *(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)*

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the grade (severity); 2) the relationship to the study therapy (attribution); and 3) the prior experience (expectedness) of the adverse event.

Adverse events (AE) refer to any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

Protocol-defined and serious AE will be collected for 28 days following the first study drug dose, or death, whichever comes first. In addition, patients with drug related AE will be monitored until symptom resolution, even if the symptoms extend beyond the 28-day period.

AEs may include:

- Exacerbation (i.e., an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the CRF and only be reported as an AE if there is an increase in frequency or severity of the condition during the study.
- Intercurrent illnesses with an onset after administration of study drug begins.

AEs DO NOT include:

- Any medical condition or laboratory abnormality with an onset date before initial study treatment is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.
- Medical or surgical procedures (the condition that leads to the procedure is the AE)
- Situations where an untoward medical occurrence has not taken place. For example:
  - Planned hospitalizations due to pre-existing conditions, which have not worsened.
  - Hospitalizations that occur for procedures not due to an AE.
  - Hospitalization for the diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (i.e. chemotherapy).

Laboratory findings DO NOT need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at screening.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g., in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- An abnormal laboratory value that cannot be confirmed after repeat analysis,

preferably in the same laboratory.

8.2.2 Serious Adverse Events

All serious adverse events (SAEs) regardless of causality to study drug, will be reported to the Principal Investigator within 24 hours of first awareness of the event. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs will be reported to the IRB per current institutional standards. In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A. The Michigan IND/IDE Assistance Program (MIAP) will assist the Sponsor in submitting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32.

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

A serious adverse event (SAE) is any adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect and/or is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Life-threatening is defined as an adverse event or suspected adverse reaction in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.
- Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the subject's medical history at the time of signing informed consent form should not be considered SAEs.
- Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure)

should not be considered SAEs. However, if the preexisting condition worsened during the course of the study it should be reported as an SAE.

8.2.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the IB.

8.2.4 Unexpected Adverse Events

Unexpected is defined as an adverse event or suspected adverse reaction that is not listed in the IB or Package Insert (Label) or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the National Cancer Institute (NCI) CTCAE version 5 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be downloaded from the Cancer Therapy Education Program (CTEP) web site. *(http://ctep.cancer.gov;https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)*.

If CTCAE grading does not exist for an AE, the PI is responsible for assigning a severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 to 4, as defined here:

- Mild: The AE is of little concern to the subject. The event is not expected to have any effect on the subject's health or well-being.
- Moderate: The subject has enough discomfort to cause interference with or change in usual activities. The event is of some concern to the subject's health or well-being. The event may require medical intervention.
- Severe: The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up.
- Life-threatening: life-threatening consequences; urgent intervention indicated.

8.3.2 Attribution of the AE

The investigator or co-investigator listed on the 1572 is responsible for assignment of attribution. The relationship of each AE to the study drug will be assessed using the following definitions:

Table 6: Definitions of AEs

	Term	Definition
Related	Probable	The AE is likely related to the study drug. The temporal relationship between the event and the administration of the study drug is compelling, and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, concomitant therapies, or accident.
	Possible	The AE may be related to the study drug. There may be some temporal relationship between the event and the administration of the study drug but there remains some ambiguity as to the cause.
Unrelated	Unlikely	The AE is doubtfully related to the study drug. The current knowledge or information about the AE indicates that a relationship to the study drug is unlikely.
	Unrelated	The AE is clearly NOT related to the study drug. The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no obvious temporal relationship exists between the investigational product and the event.

For the purposes of this study, 'Related' shall mean 'Probable' and 'Possible' relationship to drug as determined by the PI.

In the absence of information on causality from the reporting investigator, the Sponsor will consult the reporting investigator and encourage an opinion on this aspect.

The outcome of the AE may be classified as follows:

- Resolved: The subject has fully recovered from the event with no residual effects observable.
- Resolved with sequelae: The subject has fully recovered from the event with residual effects observable.
- Ongoing: Effects of the event are present and changing. The event is not considered stabilized or resolved.
- Death: The event was the primary cause of death (may or may not be the immediate cause of death).

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

8.4 Serious Adverse Event Reporting Guidelines

All serious adverse events (SAEs) regardless of causality to study drug, will be reported to the Principal Investigator within 24 hours of first awareness of the event. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All Serious Adverse Events will be reported to the IRB per current institutional standards.

In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A. The Michigan IND/IDE Assistance Program (MIAP) will assist the Sponsor in submitting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32.

The original copy of the SAE Report Form and the fax confirmation sheet or email must be kept with the subject documentation at the study site. Follow-up information should be sent using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re- occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from trial participation.

Reporting to GlycoMimetics, Inc.

As the holder of the IND for the Study, University of Michigan Sponsor-Investigator, Lena Napolitano, MD will be responsible for all required regulatory reporting obligations and will submit IND Safety Reports to the FDA in accordance with applicable laws and regulations.

Reports will be submitted to GlycoMimetics, Inc. by the following guidelines:

- Sponsor-Investigator will send a final copy of all Suspected Unexpected Serious Adverse Reaction (SUSAR) reports (i.e., IND Safety Reports) to GlycoMimetics, Inc. in parallel to submission to FDA.
- Sponsor will send a final copy of all Serious Adverse Event reports to GlycoMimetics, Inc. within 15 days of Sponsor awareness of the event.
- All SAE and SUSAR reports will be e-mailed to IQVIA Biotech: Safety-inbox.biotech@iqvia.com

Any additional information pertaining to the SAE and SUSAR, including complications, progression of the initial event, and recurrent episodes, will be reported as follow-up to the original episode.

8.4.1 Principal Investigators Should be Notified of any Serious Adverse Events

Lena M. Napolitano, MD, FACS
Director, Surgical Critical Care
Department of Surgery, 1C340-UH, SPC 5033
1500 East Medical Center Drive
Ann Arbor, MI 48109-5033
Telephone: 734-615-4775
Email:lenan@umich.edu

Suman Sood, MD
University of Michigan Hemophilia and Coagulation Disorders Program
Phone: 734-615-2681
Pager: 17132
Email: sumisood@med.umich.edu

8.5 Routine Reporting

All other adverse events, such as those that are expected, or are unlikely or unrelated to the drugs administered, are to be reported to the IRB annually as part of regular data submission.

8.6 Reporting of Unanticipated Problems

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience, or outcomes is considered unanticipated if it meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency);
- Related or possibly related to participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.7 Pregnancies

Pregnancy occurring in a female subject or a male subject's partner during the trial period will be documented in the subject's source documents and reported on a Pregnancy Form to the SAE hotline and to the IRB by the investigational staff within 1 working day of their knowledge of the event. Pregnancy itself is not an AE; it should be reported for tracking purposes. The PI or designee will discontinue the pregnancy subject from the treatment aspects of the trial, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs/SAEs.

The study staff will request the pregnant subject to notify the study site of the outcome of the pregnancy (i.e., birth, loss or termination). To help ensure this, the study site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

9 DRUG INFORMATION

9.1 Uproleselan Injection, 50 mg/mL

Other Names for the Drug: GMI-1271

Description: Uproleselan injection is a sterile solution for IV administration, supplied in single-dose vials at a concentration of 50 mg/mL.

Classification - Type of Agent: small molecule E-selectin antagonist

Mode of Action: E-selectin antagonist

Pharmacokinetics: PK evaluations in healthy volunteers showed a dose-linear relationship in mean PK parameters after IV infusion of uproleselan 2 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, and 40 mg/kg. Uproleselan is characterized by a half-life of 1.4 to 2.5 hours and does not accumulate after doses up to 20 mg/kg twice daily. Population PK analysis in healthy volunteers and subjects with AML demonstrates similar PK profiles, PK parameters, and dose-proportionality. Clearance was found to depend on renal function and have a similar magnitude in both healthy volunteers and in subjects with AML. Clearance is not dependent on body size which allows for flat-fixed dosing. The PK of uproleselan does not appear to be affected when co-administered with chemotherapy. Uproleselan is predominantly (>95%) excreted unchanged in the urine and is not extensively metabolized in humans. Refer to the uproleselan IB for further information.

Side Effects: No adverse events were seen during pre-clinical testing. The safety and efficacy of uproleselan have not been fully established. However, limited human safety information is available from Phase 1 clinical trials in healthy volunteers and subjects with DVT, MM, and a Phase 1/2 clinical trial in subjects with AML. No specific toxicities, or target organs for toxicity, have been identified thus far in nonclinical studies or in clinical trials for uproleselan. This includes administration alone or with cytarabine-based chemotherapy regimens for AML. In healthy volunteer studies, no trends in routine lab evaluation such as hematology, chemistry, coagulation, urinalysis, electrocardiogram (ECG) and bleeding time were observed. Clinical trials are ongoing. Refer to the uproleselan IB for further information.

Drug Interactions: No known drug interactions

Uproleselan (GMI-1271) Supply and Storage

Uproleselan must be received by designated staff at the trial site, handled and stored safely and properly, and kept in a secured location to which only the designated staff (i.e., pharmacist) have access. Upon receipt, uproleselan should be stored frozen according to the instructions specified on the labels and in the IB and pharmacy reference manual.

The investigator must not store uproleselan at, nor dispense it from, any location other than that agreed upon with the sponsor and approved by the IRB.

The lot numbers for the supplied uproleselan will be provided to the trial site with the trial drug shipment. Uproleselan batch certificates are available at the request of site personnel.

Uproleselan (GMI-1271) Packaging and Labeling

GlycoMimetics will provide uproleselan to the pharmacist in labeled containers. Vials containing uproleselan will be packed into cartons containing a specific number of vials per carton. A tamper-evident seal will be placed on each carton. All vial and carton labels will meet applicable local regulatory requirements.

Uproleselan (GMI-1271) Preparation, and Administration

Uproleselan injection 50 mg/mL is stored per the specified conditions on the label, frozen (-10 °C to -25 °C), prior to administration. The frozen product can appear as a homogenous solid, a striated solid, or as a super-cooled liquid. When using frozen supply, vials should be brought to room temperature before dose preparation. Upon thawing, the product should be gently inverted 4 to 5 times to ensure homogeneity of the solution. The thawed solution is clear, colorless to slightly yellow, and free from visible particulates.

Uproleselan should be administered IV into a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC). Infusion should take place at a steady rate over a period of 20 minutes (±2 minutes) using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration is highly recommended. Dilution of uproleselan may be performed with normal saline (0.9% Sodium Chloride) up to 5X as needed for ease of administration and per institutional practice. Compatibility with other therapeutic agents has not been determined; therefore, uproleselan injection should be administered via a separate IV line and should not be administered concurrently with anything other than saline. If a flush is used, saline flush is preferred.

When prepared in syringes or intravenous (IV) bags without an administration set attached, uproleselan may be stored refrigerated up to 72 hours prior to administration or up to 24 hours at controlled room temperature prior to administration. Administration sets manufactured from materials of construction other than polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP) can be primed up to 72 hours before dosing if stored refrigerated or up to 24 hours before dosing if stored at controlled room temperature. Intravenous lines consisting of PVC with DEHP should be avoided when possible. If PVC with DEHP administration sets must be used, they should be primed with uproleselan solution no more than 2 hours before dosing. It is highly recommended that uproleselan prepared prior to administration be refrigerated until 1 hour prior to dosing.

Uproleselan will be administered intravenously to the subject by authorized site personnel only. It is critical that both the start and end times of uproleselan administration are accurately recorded in the site records when possible and available.

Uproleselan is to be kept in a locked and secured storage facility, accessible only to those individuals authorized by the principal investigator (PI).

Clinical Supply Accountability

The investigator and trial staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following instructions in the pharmacy reference manual and adhering to Good Clinical Practice (GCP) guidelines.

Under no circumstances will the investigator and trial site staff allow the uproleselan to be used other than as directed by this protocol. Uproleselan will not be dispensed to any individual who is not enrolled in the trial.

An accurate and timely record of clinical supplies must be maintained. This includes but may not be limited to: (a) documentation of receipt and condition of uproleselan, (b) documentation of uproleselan dispensing/return to/from pharmacy, and (c) documentation of destruction/return of uproleselan to GlycoMimetics (or designee). All uproleselan must be accounted for and all discrepancies investigated and documented appropriately.

If required, at trial close-out and as appropriate during the course of the trial, the investigator will return all unused uproleselan, packaging, labels, and a copy of the completed accountability logs to the GlycoMimetics (or designee) for drug return or destruction.

Uproleselan (GMI-1271) Disposal and Destruction

Upon written approval, and after accountability has been confirmed, the unused supply of uproleselan can be destroyed at the trial site per local guidelines, by a third party, or returned to the GlycoMimetics' designee as appropriate.

Misuse, Overdose, and Medication Error

Misuse, overdose, or medication errors (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8

Note: The 24-hour reporting requirement for SAEs does not apply to reports of investigational medicinal product unless these result in a SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

Misuse – Intentional use of investigational medicinal product other than as directed or indicated at any dose.

Overdose – Intentional or unintentional intake of a dose of an investigational medicinal product exceeding a pre-specified total daily dose of the investigational medicinal product. The adverse experiences associated with the overdose should be reported as other serious reactions.

Overdose will be defined as:

- Total administered over a 24-hour period: >5500 mg

Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational medicinal product.

Distribution Site:

CSM Holdings Inc.

342 42nd St S
Fargo, ND 58103

10 CORRELATIVES/SPECIAL STUDIES

10.1 Sample Collection Guidelines

The total volume of plasma needed for the assays listed below is 1ml (in one 2.7 ml sodium citrate vacutainer tube). The blood will be spun down at 2500xg for 20 minutes at 4degrees C, and then the plasma snap frozen in liquid nitrogen and then stored at -80degrees C.

10.2 Assays to be Performed on Samples

TNF-alpha
soluble E-selectin
soluble P-selectin
Interleukin-6 (IL6)
Interleukin-10 (IL-10)
Angiopoietin-2

Blood will be collected only via direct venipuncture at the time points delineated in Section 6.2: Study Schedule of Events

10.3 Assay Methodology

Commercial ELISA assays will be used to evaluate **TNF-alpha**, **soluble E-selectin, soluble P-selectin**, **Interleukin-6 (IL-6)**, **Interleukin-10 (IL-10), TNF-alpha and Angiopoietin-2**.

Whole blood will be drawn and centrifuged based on company protocols.[26, 43] Plasma will be drawn off, aliquoted, snap frozen, and stored at −80°C. Biomarkers analyzed by ELISA for protein determination include soluble E-selectin (Ebiosciences, now Thermo Fisher Scientific, Waltham, MA, USA); soluble P-selectin, interleukin-10, interleukin-6, TNF-alpha and angiopoietin-2 (Thermo Fisher Scientific, Waltham, MA, USA). ELISA assays will be performed using centrifuged citrated blood according to protocol. Samples will be run in duplicate according to manufacturer's instructions.

11 SPECIMEN BANKING

Subject samples collected for this study will be retained at the Conrad Jobst Vascular Research Laboratory. Samples may be used for additional testing of the Correlative/Special Studies as feasible with plasma remaining after all testing is complete. Any data obtained from the use of clinical specimens will be the property of the University of Michigan and GMI for publication and any licensing agreement will be strictly adhered to.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design/Study Endpoints

This is a prospective, interventional, single-arm, open label trial, with 1:1 matched de-identified retrospective control cohort. Study subjects will receive uproleselan IV BID x 7 days. 15 patients who consent to drug administration will be enrolled in the treatment arm.

Primary Endpoints: Safety

12.1.2. Additional Interim Safety Assessment (Study Sample Size: 15 patients)

An interim assessment for toxicity and early mortality will be performed after the first 5 patients have enrolled, and again after the first 10 patients are enrolled. Accrual may proceed to a maximum of 15 patients, if the stopping rules are not met within the first 5 patients.

12.1.3. Secondary Endpoints

- Reduction in the progression to acute respiratory failure [Time Frame: 15 days]
- Patients with a baseline PaO2/FiO2 >= 200: progression of respiratory failure is defined by:
  a. severe gas transfer deficit (PaO2/FiO2 < 200);
  b. persistent respiratory distress while receiving oxygen (persistent marked dyspnea, use of accessory respiratory muscles, paradoxical respiratory movements);
  The rate will be calculated as the proportion of patients who experienced at least one of the events above by day+15 from treatment start.
- Overall survival and all-cause mortality (day 15, day 28).
- Time to improvement in oxygenation for at least 48 hours. Improvement in oxygenation is defined as an increase in PaO2/FiO2 of 50 (or greater) compared to the nadir of PaO2/FiO2.
- Number of patients requiring mechanical ventilation, if not on mechanical ventilation at study entry.
- Reduction in progression to acute respiratory failure [Time Frame: 28 days]
- Change in the WHO COVID-19, "8-point ordinal scale" from study entry to day 28 (Table 1). To be assessed on day 3, day 8, day 15, day 28.
- Duration of hospitalization and duration of ICU care.
- Toxicity assessment (including incidence of grade 3-5 hemorrhagic events).
- Change in D-dimer [Time Frame: baseline, study day 3, day 8, day 15, and day 28]. Changes in plasma D-dimer level compared with baseline at enrollment.
- Decrease or Change in IL-6:IL-10 ratios.
- Free-Days- at day 28
  - Oxygen
  - Ventilator
  - Vasopressor
  - ICU
  - Hospitalization

Table 1: WHO Ordinal scale Ordinal Score:

Patient State	Descriptor	Score
Ambulatory	No limitation of activities	1
	Limitations of activities	2
Hospitalized (mild disease)	No oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized (severe disease)	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Mechanical ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Exploratory Endpoints

- Soluble E-selectin and P-selectin levels compared with baseline at enrollment.
- Thrombosis free days (clinically defined) at day 28.
- Change in other cytokine levels, endothelial or leukocyte activation (day 1, 15, 28) in IL-6, IL-10, TNF-alpha and Angiopoietin-2.

12.2 Sample Size and Accrual

This is a pilot proof of concept feasibility study. 15 patients who consent to drug administration will be enrolled in the treatment arm.

The sample size determination was not based on statistical power analysis but is large enough to provide adequate information regarding safety, and to contribute to the design of subsequent studies, and is the number of patients that we can expect to accrue in the current setting of the SARS-CoV2 pandemic.

12.3 Data Analyses Plans

Descriptive statistics will be calculated for quantitative safety data, as well as change from baseline. Frequency counts will be compiled for classification of qualitative safety data.

Secondary endpoints include reduction in the progression to acute respiratory failure. For patients with a baseline PaO2/FiO2 >= 200: progression of respiratory failure is defined by:

a. severe gas transfer deficit (PaO2/FiO2 < 200);
b. persistent respiratory distress while receiving oxygen (persistent marked dyspnea, use of accessory respiratory muscles, paradoxical respiratory movements);

The rate will be calculated as the proportion of patients who experienced at least one of the events above by day+15 from treatment start.

There are many other secondary endpoints, but two of the most important are: (i) Day 28 overall survival and (ii) Day 28 ventilator free survival, both of which are binary endpoints. Day 28 overall survival will be summarized by the proportion of the twelve patients who are alive at Day 28 after starting treatment, and Day 28 ventilator-free survival will be summarized by the proportion of the twelve patients who are both alive and not using a ventilator at Day 28 after starting treatment. Both proportions will be

accompanied by an exact 95% confidence interval. All other secondary endpoints will be collected and assessed.

13 STUDY STOPPING RULES

Additional Interim Safety Assessment (Study Sample Size: 15 patients)

An interim assessment for toxicity and early mortality will be performed after the first 5 patients have enrolled, and again after the first 10 patients are enrolled. Accrual may proceed to a maximum of 15 patients, if the stopping rules are not met within the first 5 patients

The study may be halted for further review if, for any reason involving subject safety, the PIs and Medical Monitors deem continuing the study inappropriate. The following scenarios will also result in temporarily halting the study for further review: 1) major bleeding event in more than 2 of first 10 patients on protocol (as defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 2g/dL or more, or leading to transfusion of two or more units of whole blood or red cells). This bleeding definition is congruent with International Society of Thrombosis and Hemostasis (ISTH) definition of major bleeding. An incidence of > 20% hemorrhagic complications would be unacceptable in this setting. Thus, we will continually monitor the observed proportion of patients with major bleeding complications. We start with prior Beta distribution, which has mean 0.2. If ever we have more than 80% posterior probability that the true proportion is greater than 0.20, accrual to the protocol will be suspended to allow the MM and PIs to review the incidence of major bleeding. 2) We will also continually monitor the study for excessive Day 15 mortality. In parallel with our decision rule related to excessive severe hemorrhagic events, we will suspend accrual if we see if we see at least five deaths by Day 15 among the first six patients, or at least seven deaths by Day 14 among the first eleven patients. If the true Day 14 mortality rate is 70% (which is the historical rate for patients with respiratory compromise), the study has a probability of 0.80 of being suspended. Conversely, if the Day 14 mortality rate is 50%, the study has a much lower probability of 0.30 of being suspended.

In the event of temporary halt of the study, the PI's, medical monitor, and independent medical monitor will meet to review the data and discuss relatedness to study drugs and determine next necessary steps. If the study is halted or terminated, a written statement fully documenting the reasons for study halt or termination and subsequent decisions of study execution will be communicated to the IRB and appropriate regulatory authorities.

14 DATA AND SAFETY MONITORING

The Data Safety and Monitoring Plan (DSMP) will consist of an independent Medical Monitor (a physician from UMHS) who will work with the PIs to evaluate AEs. The Investigators and Medical Monitors will perform ongoing review of all SAEs in a timely fashion, and regular reviews of all clinical data (including AEs and lab data) throughout the study. Any concerns for safety by any of these parties will be communicated to the other parties immediately for discussion. The investigators and co-investigators will meet monthly during the study and will allocate adequate time for such monitoring activities. They will review expected and unexpected adverse events, safety concerns, adherence to protocol therapy, study enrollment, and any potential protocol amendments that may be required. Recommendations for study continuation, amendments, suspension and/or study termination will be made at each of the monthly protocol monitor meetings.

The investigators will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study- related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. If while following the Data Safety and Monitoring Plan (DSMP), as outlined in Section 8.5, there is a pattern of unexpected and concerning AE or a SAE then, there would be a consideration to create a Data and Safety Monitoring Board (DSMB).

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