Study Protocol:

Open-label study of Maraviroc in Hospitalized Individuals Diagnosed with SARS-CoV-2

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Clinical Research Protocol

OPEN-LABEL STUDY OF MARAVIROC IN HOSPITALIZED INDIVIDUALS DIAGNOSED WITH SARS-COV-2

Version Date:	11/6//2020
Commercial Product:	Maraviroc
IND Number:	PIND 150411, IND exempt
Development Phase:	Phase 1
Sponsor:	Department of Medicine
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TITLE	Open-Label Study of Maraviroc in Hospitalized Individuals Diagnosed with SARS-CoV-2
PRINCIPAL INVESTIGATOR	Philip A. Chan MD, MS
SPONSOR	Department of Internal Medicine
SITE	Rhode Island Hospital The Miriam Hospital
RATIONALE	CCR5 antagonism in SARS-CoV-2 may alter cell trafficking of inflammatory cells, reduce activation of platelets, and may have a role in reversing lymphopenia. Maraviroc may also have anti-viral properties related to binding to SARS-CoV-2 Main Protease beyond its mechanism as a CCR5 antagonist.
STUDY DESIGN	Single-arm, Open-Label, Proof-of-Concept
PRIMARY OBJECTIVE	To establish whether Maraviroc, used at its approved dosage for HIV, is safe and effective in hospitalized patients with SARS-CoV-2.
SECONDARY OBJECTIVES	Investigate the relationship between reduction of inflammatory and other biomarkers (such as IL-6, CCL5, etc.) later in the course of infection and avoidance of respiratory decompensation and death.
NUMBER OF SUBJECTS	16 subjects
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • Male or female ≥ 18 years of age at time of screening • Documentation of a SARS-CoV-2 diagnosis as evidenced by positive SARS-CoV-2 PCR within twelve days at time of screening • Chest radiography consistent with multi-focal pneumonia or air-space disease • Written informed consent obtained from subject and ability for subject to comply with the requirements of the study. • Subject able to safely swallow pills or receive Maraviroc through a nasogastric or orogastric tube. Exclusion Criteria: • Subjects who are pregnant, breastfeeding, or unwilling to practice birth control during participation in the study. • Subjects with the presence of a condition or abnormality that in the opinion of the Investigators would compromise the safety of

	the patient or the quality of the data. This includes, but is not limited to, recent myocardial infarction in past 6 months, neurological, psychiatric, endocrine, or neoplastic diseases that are judged to interfere with participation in the study. • Subjects with known diagnosis of human immunodeficiency virus infection (HIV) • Subjects enrolled in another interventional trial (including one for COVID-19) that excludes participation in other trials or includes a potent CYP3A inhibitor or inducer (e.g. lopinavir-ritonavir). • Subjects with ESRD or severe renal failure who are taking potent (moderate or strong) CYP3A inhibitors or inducers
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Maraviroc will be administered orally twice daily for seven days.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 35 days Treatment: 7 days Follow-up: 28 days The total duration of the study is expected to be 4 months. 2 months for subject recruitment, 1 for final subject follow-up and 1 month for data run-off and analysis.
CONCOMMITANT MEDICATIONS	Prohibited: Lopinavir-Tenofovir Hydroxychloroquine Ivermectin
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• In this proof-of-concept trial, the study team is chiefly concerned with safety and tolerability of Maraviroc in subjects diagnosed with SARS-CoV-2. The primary endpoint is rate of subjects who complete the 7-day course of Maraviroc without discontinuation for serious adverse event or death. Additional endpoints include the percent of study population reaching clinical improvement, defined as time from enrollment to an improvement of two points on a seven-category ordinal scale (defined below), at Day 7.
SECONDARY ENDPOINTS	• Time to improvement to Score of 2 or less (Days) based on Ordinal scale: **1**, not hospitalized with resumption of normal activities; **2**, not hospitalized, but unable to resume normal

	activities OR hospitalized pending disposition, not requiring COVID-related care; **3**, hospitalized, not requiring supplemental oxygen; **4**, hospitalized, requiring supplemental oxygen; **5**, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; **6,** hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and, **7,** death. • Change in biomarker levels (CCL5, IL-6, Chi311, etc) from time of enrollment to completion of therapy or live discharge from the hospital (whichever comes first) • 7-, 14- and 28-day all-cause-mortality • Days on mechanical ventilation
SAFETY EVALUATIONS	Daily, multi-disciplinary safety monitoring with interim analysis after 8 subjects have received four or more doses of Maraviroc.
PLANNED INTERIM ANALYSES	Exposure-adjusted rates of adverse events and those resulting in discontinuation will be calculated at the point in which 8 patients have received more than four doses of treatment. Serious adverse events will be monitored by the study team on an ongoing basis throughout the study.
STATISTICS **Analysis Plan**	• Rates of adverse events by severity and rate of completion of therapy. • Change in biomarkers compared to clinical improvement • Percent of study population reaching clinical improvement at Day 7 will be compared to published results from Remdesivir for 5 or 10 Days in Patients with Severe COVID-19, and other available clinical trials including The Randomized Evaluation of COVID-19 therapy (RECOVERY) Trial.

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1 BACKGROUND

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of Coronavirus disease 2019 (COVID-19) and was first reported in Wuhan, China in December 2019[1]. Though a wide spectrum of clinical manifestations exists, patients often present with mild upper respiratory symptoms, progressing in some cases to a multifocal pneumonia with multiorgan compromise[2]. As the natural history of SARS-CoV-2 is further understood, increased attention has been devoted to understanding disease progression and notably severe respiratory complications which are described as occurring after 7-14 days after the onset of illness. Initial retrospective studies of confirmed COVID-19 cases in tertiary hospitals in Hubei Province, China, revealed a range of 1-20 days for the progression of respiratory distress following illness onset[1,2,3.] The clinical course of COVID-19 infections appears to have a high degree of heterogeneity, with some remaining relatively uncomplicated, some progressing to a moderate pneumonia, and others developing severe, progressive pneumonia characterized by dyspnea, tachypnea, and hypoxia. Increased levels of IL-6 and decreased levels of lymphocytes have been reported in severe illnesses in a retrospective cohort of patients from Jinyintan and Wuhan hospitals. Older age and common comorbidities including hypertension, diabetes, and coronary artery disease have been associated with increased mortality[3].

In the negative randomized, controlled, open-label trial of Lopinavir-Ritonavir involving patients with COVID-19 and oxygen saturation of less than 94% on room air, 70% of patients required supplemental oxygen and 15% required high-flow nasal cannula or non-invasive mechanical ventilation on presentation. Only one patient required intubation on presentation, but 16% would eventually require mechanical ventilation during their hospitalization. At Day 7, only 6% of the subjects in the Lopinavir-Ritonavir reached clinical improvement of 2 points on a 7-point ordinal scale. At day 14, 45.5% of subjects reached 2-point clinical improvement, 15.2% of subjects had died, and 28% continued to require non-invasive and nasal cannula support. This early study highlighted the lengthy duration of hospitalization and late progression of respiratory failure in COVID-19. [4]

SARS-CoV-2 is an RNA coronavirus that enters the cell through an endosomal route, during which the virus attaches to Angiotensin-Converting-Enzyme-2 receptor, subsequently endocytosed into a vesicle and released into the cytoplasm of the cell via cathepsin-cleaved spike protein. The virus can also attach to Transmembrane Serine Protease 2 (TMPRSS2) to directly enter the cell via fusion with the cell membrane. Once in the cell the viral mRNA is transcribed via RNA-dependent RNA polymerase to create more

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[1] Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/NEJMoa2001316

[2] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

[3] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

[4] Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19 N Engl J Med. 2020. doi:10.1056/NEJMoa2001282

genome RNA. Additionally, sub-genomic mRNAs are translated to create proteins including proteases and replicates, such as papain-like protease, 3C-like protease (also known as main protease) and RNA-dependent DNA polymerase (RdRp). [5]These proteins serve as potential targets for anti-virals. Remdesivir, an anti-viral that received FDA Emergency Use Authorization for use in COVID-19, targets RdRp. Other FDA approved medications have been identified as potential drugs to re-purposing. Virtual screening of 2388 FDA approved medications for binding affinity to the SARS-CoV-2 3C-like protease (main protease), which is essential for processing the polyproteins required for viral assembly, revealed the CCR5-antognist Maraviroc to have the second-highest binding affinity. Further molecular conformational dynamic simulations and the MMPBSA approach are ongoing to provide further estimation of the binding affinity of Maraviroc to binding site on the 3C-like protease.[6]

A growing body of literature is addressing the complex pathophysiology underlying COVID-19 infections to better understand human responses to the novel coronavirus. Given the similarities between other coronaviruses, including SARS-CoV-1, and SARS-CoV-2, pathogenesis of SARS-CoV-2 has been extrapolated from SARS-CoV-1 disease in animal models. In senescent mouse models of SARS-CoV-1 infection, increased expression of chemokine mRNA was observed in the lungs early and late in the infection, in a "biphasic" manner. Compared to controls, a >9-fold increase in CCL5/RANTES and 4-fold increase in CCR2 mRNA were detected around days 7-9 of infection, when histopathologic evidence of pneumonitis was noted. Additionally, inflammatory cells recruited to the lungs early and late in the infection corresponded to the biphasic expression of aforementioned chemokines.[7]

CCR5 antagonism may play a role in diminishing acute lung injury correlating to chemotaxis of neutrophils and other effector cells late in the course of Coronavirus infection. Mouse models of acute lung injury have demonstrated that treatment with a CCR5 antagonist, Maraviroc, significantly reduced lung neutrophil infiltration, inhibited lung edema formation, and prevented histological tissue alterations.[8] In addition, in-vitro studies of Maraviroc have demonstrated its ability to effectively inhibit macrophage and dendritic cell chemotaxis.[9]

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[5] Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. Antiviral Res. 2013;100(3):605-614. doi:10.1016/j.antiviral.2013.09.028

[6] A. Shamsi, T. Mohammad, S. Anwar, F. MohamedAl Ajmi, A. Hussain, M.T. Rehman, A. Islam, M.I. Hassan Glecaprevir and Maraviroc are high-affinity inhibitors of SARS-CoV-2 main protease: possible implication in COVID-19 therapy. *Bioscience Reports*, 40 (2020) 10.1042/BSR20201256

[7] Chen J, Lau YF, Lamirande EW, et al. Cellular Immune Responses to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection in Senescent BALB/c Mice: CD4+ T Cells Are Important in Control of SARS-CoV Infection. *J Virol*. 2010;84(3):1289-1301. doi:10.1128/jvi.01281-09

[8] Grommes J, Drechsler M, Soehnlein O. CCR5 and FPR1 mediate neutrophil recruitment in endotoxin-induced lung injury. *J Innate Immun*. 2014;6(1):111-116. doi:10.1159/000353229

[9] Rossi R, Lichtner M, De Rosa A, et al. In vitro effect of anti-human immunodeficiency virus CCR5 antagonist maraviroc on chemotactic activity of monocytes, macrophages and dendritic cells. *Clin Exp Immunol*. 2011;166(2):184-190. doi:10.1111/j.1365-2249.2011.04409.

Chitinase 3-like 1 (Chi3l1, also called as YKL-40) is a powerful inhibitor of epithelial cell death and oxidant induced lung injury. Mice that lack Chi3l1 are particularly susceptible to the ravages induced by hyperoxia and other exposures that induce Acute Lung Injury (ALI).[10] Studies have demonstrated that the expression levels of Chi3l1 in the lung were significantly decreased by the RIG-like helicase (RLH) immune activation, the well-defined host sensing mechanism of RNA viruses like SARS-CoV-2.[11] These studies may suggest that the expression levels of Chi3l1 can be used as a sensitive biomarker of SARS-CoV-2 infection that predict disease severity and progression.

Recognizing that the relationship between the immune response and chemokine signaling are dynamic and complex, studies are needed to explore CCR5 antagonism as a possible therapeutic target for SARS-CoV-2 infections. This study proposes that CCR5 antagonism prior to the second wave of inflammatory mediator expression may reverse lymphoid depletion and may alter cell trafficking of inflammatory cells, both increasing viral control capacity and dampening damage to lung tissue, respectively.

2 STUDY RATIONALE

This pilot study seeks to establish that selective blockade of the CCR5/CCL5 axis as well as the potential anti-viral properties of Maraviroc may reduce disease severity. This proof-of-concept effort seeks to correlate differences in clinical outcomes to differential cytokine expression in the setting of CCR5 antagonism in patients infected with SARS-CoV-2. Maraviroc is FDA-approved for the treatment of CCR5-tropic HIV-1 and has a well-documented safety and tolerability record in previous trials in immunocompromised HIV patients. Maraviroc was not shown to have significant effect on the QT segment, can be delivered via oral formulation, and can be delivered safely to both patients with end-stage renal disease and dependence on hemodialysis[12]. For these reasons, Maraviroc is an ideal candidate to study as a potential therapy for hospitalized patients with moderate-to-severe COVID-19.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to establish whether Maraviroc, used at its approved dosage for HIV, is safe, tolerable, and effective in hospitalized patients with SARS-CoV-2.

[10] M. H. Sohn et al., The chitinase-like proteins breast regression protein-39 and YKL-40 regulate hyperoxia-induced acute lung injury. Am J Respir Crit Care Med 182, 918-928 (2010).

[11] B. Ma et al., RIG-like Helicase Regulation of Chitinase 3-like 1 Axis and Pulmonary Metastasis. Sci Rep 6, 26299 (2016).

[12] Vourvahis M, Fang J, Checchio T, et al. Pharmacokinetics, safety, and tolerability of maraviroc in HIV-negative subjects with impaired renal function. *HIV Clin Trials*. 2013;14(3):99-109. doi:10.1310/hct1403-99

3.2 Secondary Objectives

The secondary objective is to investigate the relationship between reduction of inflammatory markers (such as IL-6, CCL5, etc.) and clinical outcomes, including avoidance of respiratory decompensation and death.

4 STUDY DESIGN

4.1 Study Overview

This is a single-center, single-arm, open-label trial. Sixteen hospitalized patients will be enrolled. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be approached for consent prior to entering the study. Each subject will receive 7 days of Maraviroc twice daily. Each subject will have blood samples checked at time of enrollment (Day 0), Day 3, Day 7, and Day 15 or time of live discharge (whichever comes first) of the study. The total duration of subject participation will be five weeks. The total duration of the study is expected to be 16 weeks.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoint

This proof-of-concept trial will evaluate safety and tolerability of Maraviroc in SARS-CoV-2 infected patients. The primary endpoint is rate of patients who complete the 7-day course of Maraviroc without discontinuation for adverse events, hospitalization, or death. Additional endpoints include the percent of study population reaching clinical improvement, defined as time from enrollment to an improvement of two points on a seven-category ordinal scale (defined below), at Day 7.

5.2 Secondary Endpoints

- Time to clinical improvement, defined as time from enrollment to an improvement of two points on a seven-category ordinal scale (defined below) or live discharge from the hospital, whichever comes first
    - Ordinal scale: **1**, not hospitalized with resumption of normal activities; **2**, not hospitalized, but unable to resume normal activities OR hospitalized pending disposition, not requiring COVID-related care; **3**, hospitalized, not requiring supplemental oxygen; **4**, hospitalized, requiring supplemental oxygen; **5**, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive ventilation, or both; **6,** hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and, **7,** death.
- Change in cytokine levels from time of enrollment to completion of therapy or live discharge from the hospital (whichever comes first)
- 7-, 14- and 28-day all-cause-mortality
- Time to improvement to Score of 2 or less (days)
- Days on mechanical ventilation

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of SARS-CoV-2 who meet the inclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

- Male or female ≥ 18 years of age at time of screening
- Documentation of a SARS-CoV-2 diagnosis as evidenced by positive SARS-CoV-2 PCR within twelve days at time of screening
- Chest radiography consistent with multi-focal pneumonia or air-space disease
- Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.
- Subject able to safely swallow pills or receive Maraviroc through a nasogastric or orogastric tube.

6.3 Exclusion Criteria

- Subjects who are pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
- Subjects with the presence of a condition or abnormality that in the opinion of the Investigators would compromise the safety of the subject or the quality of the data. This includes, but is not limited to, recent myocardial infarction in past 6 months, neurological, psychiatric, endocrine, or neoplastic diseases that are judged to interfere with participation in the study.
- Subjects with known diagnosis of human immunodeficiency virus infection (HIV)
- Subjects enrolled in another interventional trial (including one for COVID-19) that excludes participation in other trials, or includes a potent CYP3A inhibitor of inducer (e.g. lopinavir-ritonavir)
- Subjects with ESRD or severe renal failure who are taking potent CYP3A inhibitors or inducers

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

Diligent medication reconciliation will be performed between the primary inpatient team and study team. Reduction in dose or discontinuation of CYP3A inducers/inhibitors, anti-hypertensive medications, and diuretics at time of enrollment will be considered and individualized to each subject at the discretion of the inpatient team. Remdesivir and dexamethasone, if administered outside of a clinical trial, are allowed.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Lopinavir-Tenofovir
- Hydroxychloroquine
- Ivermectin

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Up to a total of 16 individuals who have been diagnosed with SARS-CoV-2 and agree to participation in the study will be placed on Maraviroc 300 mg twice daily for 7 days.

Given design as an early, proof-of-concept trial, all patients will be assigned to the treatment group. There will be no placebo control group; however, patients who are withdrawn from the trial drug will be consented at time of enrollment about continuing biomarker surveillance at standard scheduled monitoring times (Day 0, 3, 7 and the earlier occurring timepoint of discharge or Day 15). Subjects who stop Maraviroc prior to completion of Maraviroc will not be replaced.

By definition, Day 0 is day of enrollment extending to administration of first dose of Maraviroc. Day 1 of study is day of first complete BID dosing of Maraviroc.

8.2 Formulation of Test Product

Maraviroc will be supplied in the same formulation of Selzentry, developed by ViiV Healthcare, a global specialist in HIV established in 2009 by Pfizer and GlaxoSmithKline.

8.3 Supply of Study Drug at the Site

Pfizer will reimburse for study drug obtained by Lifespan Pharmacy.

8.3.1 Dosage/Dosage Regimen

- Maraviroc 300 mg twice a day for patients not on concomitant moderate or strong CYP3A inhibitors/inducers.
- Maraviroc 150 mg twice daily for patients unable to tolerate 300 mg twice daily and for patients on moderate or strong CY3PA inhibitors.
- Maraviroc 600 mg twice daily for patients on moderate or strong CY3PA inducers.

8.3.2 Dispensing

Maraviroc will be dispensed by a Pharmacist at the trial site.

8.3.3 Administration Instructions

Maraviroc can be administered twice a day by mouth with or without food. Maraviroc can also be crushed, mixed with 60 mL sterile water, and administered through a nasogastric or orogastric tube. Documentation of administration will be recorded as per standard protocol of the inpatient unit.

8.4 Measures of Treatment Compliance

Medication Administration records from site's Electronic Medical Record will be audited daily to ensure treatment compliance.

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented during the Screening/Enrollment Visit (Day 0), during Study Days 1-8, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at enrollment.

9.1.3 Medical History

The follow will be recorded at Screening:

- Date of onset and presence of symptoms related to SARS-CoV-2 infection including cough, shortness of breath, fatigue, nausea, vomiting, diarrhea, rash, abdominal pain, fever, chills, loss of smell, etc.
- History of obesity, hemodialysis, cardiovascular diseases (hypertension, known valvular disease, cardiomyopathies and/or LV systolic or diastolic dysfunction), pulmonary disease (including OSA, COPD, asthma, interstitial lung disease, cystic fibrosis, bronchiectasis, lung transplant, lung cancer, pulmonary hypertension).

9.1.4 Physical Examination

A complete physical examination will be performed by an Investigator who is a physician at time of enrollment. As to reduce healthcare worker exposure to SARS-CoV-2, Investigators may perform an abbreviated physical exam at each visit and utilize components of the physical exam performed by a qualified staff member (MD, NP, and PA) on the primary care team.

9.1.5 Vital Signs

Measurement of body temperature, blood pressure, pulse and respirations will be performed and recorded each day of study participation per routine clinical care.

9.1.6 Oximetry

Oximetry will be measured on room air and on current oxygen-delivery device while the subjects are at rest during each visit unless deemed unsafe to subject to do so (e.g. patient requiring substantial amount of supplemental oxygen).

9.1.7 Other Clinical Procedures

- Imaging obtained as part of routine clinical care with be reviewed. These will include chest-imaging and CT imaging.
- Thromboelastography, if obtained part of routine care will also be reviewed and documented.

9.1.8 Adverse Events

Adverse event information will be elicited during each study visit. In an effort to reduce healthcare worker exposure to SARS-CoV-2, Investigators will speak with subjects over the phone prior to entering the room to perform an abbreviated physical exam. If a subject is unable to participate in a telephonic interview, an Investigator will perform an interview to elicit adverse events in the subject's room. Appropriate documentation in case report forms will reflect subjects who are unable to participate in conversation due to altered mental status or mechanical ventilation. In addition, all clinical documentation obtained by nursing staff, as per clinical policy and standards of care, will be reviewed daily for information pertaining to adverse events. Duration (start and stop dates and times), severity/grade, outcome, treatment, and relation to study drug will be recorded on the case report form (CRF) as detailed in Section 14.

9.2 Clinical Laboratory Measurements

9.2.1 Hematology

Blood will be obtained per standard of care and sent to trial site's hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential including absolute neutrophil count, absolute bands, absolute lymphocyte count) and platelet count) , serum C-reactive protein (CRP) and thromboelastography.

9.2.2 Blood Chemistry Profile

Blood will be obtained per standard of care and sent to trial site's chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, albumin, LDH, brain natriuretic peptide (BNP), D-dimer, troponin and lactate.

9.3 Research Laboratory Measurements

All samples collected during the study will be labeled with a de-identified, randomly generated specimen ID. Blood samples collected will be shipped overnight to InCell Dx at 1541 Industrial Road San Carlos, CA, 94070. InCellDx, a diagnostics company perform PBMC purification upon receiving samples, and will bank specimens to perform analysis on blood samples, including a cytokine panel that will consist of sCD40L, GM-CSF, IFN gamma, IL-2, IL-4, IL-6, IL-8, IL-10, RANTS, TNF-alpha, and VEGF. Using PBMCs, InCellDx will also perform a CCR5 Receptor occupancy analysis. If enough plasma and PBMC samples are banked, banked samples will be sent to the The Prlic Lab at the Fred Hutchinson Cancer Center near the end of the study. The Prlic Lab will perform additional flow cytometric analysis to provide insight regarding the immune subset distribution and state of activation of the immune system. Additionally, up to three 100 ul alliqots of banked plasma will be sent to The Elias Lab at Brown University, who will perform analysis on Chitinase 3-like 1(Chi3l1) at the end of the study period. Remaining specimen will be stored at InCellDx for up to six months after the end of the study, during which arrangements will be made to return remaining specimen to Lifespan/The Miriam Hospital Infection Diseases And Immunology Center. Remaining specimens will be destroyed 5 years after return to Lifespan. Until that time, these remaining specimens may be used for validation of results or may be used for further research studies.

10 EVALUATIONS BY VISIT

10.1 Screening and Enrollment Visit (Day 0)

- Review the study with the subject and obtain written informed consent
- Assign the subject a unique subject number.
- Record demographics data.
- Record relevant medical history.
- Record concomitant medications.
- Perform a complete physical examination.
- Perform a complete review of systems including symptoms of postural dizziness
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Perform and record results of blood pressure testing, including orthostatic vital signs.
- Document and review bloodwork obtained from standard clinical care (chemistry, hematology, hepatic function).
- Collect blood sample for research laboratory test(s): Biomarkers. Collect information on QTc if an electrocardiogram is performed per routine clinical care.
- Document and review chest imaging findings if performed per routine clinical care.

10.2 Visit 1 (Day 1)

- First dose of Maraviroc Administered in morning. Study member will be present for first administration
- Perform interview with patient. Document any Adverse Events.
- Document complete physical exam.
- Perform and document medications review.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.

10.3 Visit 2 (Day 2)

- Review and document Medication Administration Record for Day 1 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.

10.4 Visit 3 (Day 3)

- Review and document Medication Administration Record for Day 2 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.
- Collect blood sample for research laboratory test(s): Biomarkers.

10.5 Visit 4 (Day 4)

- Review and document Medication Administration Record for Day 3 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.

10.6 Visit 5 (Day 5)

- Review and document Medication Administration Record for Day 4 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.

10.7 Visit 6 (Day 6)

- Review and document Medication Administration Record for Day 5 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.

10.8 Visit 7 (Day 7)

- Review and document Medication Administration Record for Day 6 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.

- Perform and record vital signs
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.
- Collect blood sample for research laboratory test(s): Biomarkers

10.9 Visit 8 (Day 8)

- Review and document Medication Administration Record for Day 7 of study.
- Perform interview with patient. Record any Adverse Events.
- Document complete physical exam.
- Perform and record vital signs
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including transfer to intensive care, intubation, hospice referral.
- Document laboratory values and imaging obtained as part of routine standard of care.

10.10 Post-Intervention Follow-up (Day 9 and every third day prior to discharge)

- Perform interview with patient. Record any Adverse Events.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Record any events including hospitalization, intubation, intensive-care admission.
- Document laboratory values and imaging obtained as part of routine standard of care.
- Obtain blood samples for research laboratory test on Day 15

10.11 Day of Discharge

- Perform interview with patient. Record any Adverse Events.
- Perform and record vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Document laboratory values and imaging obtained as part of routine standard of care.
- Record discharge destination, oxygen requirement at time of discharge.
- Obtain research labwork if discharge occurs earlier than Day 15

- Schedule post-discharge phone follow-up.

10.12 Post-Discharge Follow-up (perform weekly till Day 35)

- Perform phone interview with patient. Record any Adverse Events.
- Review and document home medications.
- Review and document patient acquired vitals.
- Record any events including hospitalization, intubation, intensive-care admission.

10.13 Final Visit (Day 35)

- Inform subject this will be the final visit of the study.
- Perform interview with patient. Record any Adverse Events.
- If in hospital, record findings from abbreviated physical examination.
- If in hospital, perform and record vital signs.
- If in hospital, perform and record oximetry on room air and on current oxygen-delivering device.
- If in hospital, document laboratory values and imaging obtained as part of routine standard of care.
- If in hospital, record any events including intubation, intensive-care admission, change to comfort measures, hospice referral or transfer.

10.14 Early Withdrawal Visit (In-Hospital)

- Review and document Medication Administration Record.
- Perform and record vital signs, including orthostatic vital signs.
- Perform and record oximetry on room air and on current oxygen-delivering device.
- Document laboratory values and imaging obtained as part of routine standard of care.
- Assent to collect blood sample for clinical laboratory tests: Biomarkers at Day 3 and Day 7.
- Record any events including intubation, intensive-care admission, change to comfort measures, hospice referral or transfer.

10.15 Early Withdrawal Visit (Out-of-Hospital)

- Review and document home medications.
- Review and document patient acquired vitals.
- Document subjects' current location of care type (e.g. acute rehabilitation center).

- Record any events including intubation, intensive-care admission, change to comfort measures, change to do not hospitalize (DNH), hospice referral or transfer.

10.16 Death

- If in hospital, review and document Medication Administration Record. Document laboratory values and imaging obtained as part of routine standard of care.
- Review and document time and cause of death.
- Inform IRB of subject death.
- Record any preceding events including hospitalization, intubation, intensive-care admission, change to comfort measures, hospice referral or transfer.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not it is related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The study team will probe, via discussion with the subject, for the occurrence of AEs during each subject encounter and record the information in the site's source documents. Adverse events will be recorded in the patient case-report form. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment, and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. Only for the specific Adverse Event of change in liver enzymes will The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 be used. If the experience is not covered in the modified criteria, the guidelines shown in Table 2 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 2. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 3. In delineating AE relationship, research team will consider adverse events temporally or otherwise clearly related to administration of the drug in relation to noted deviation from natural history of SARS-CoV-2 infection.

Table 3. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience

- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per Lifespan IRB guidelines. The collection period for all SAEs will begin after informed consent is obtained and 28-days after last administration of Maraviroc.

In accordance with the Pfizer contractual terms, standard operating procedures and policies of the Lifespan Institutional Review Board (IRB) the Investigator or one of the study members will report SAEs to the IRB. SAE and AE documentation will occur in REDCap.

11.3 Medical Monitoring

Dr. Timothy Flanigan should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (401) 639-2433

Pager: (401) 350-5056

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment, including stoppage criteria for orthostatic hypotension
- Protocol violation requiring discontinuation of study treatment
- Drug supplier (Pfizer) request for early termination of study, after which study drug cannot be reasonably provided to subjects at no cost to them
- Positive pregnancy test (females)
- Pursuit of comfort measures only, inpatient hospice referral or transfer to inpatient hospice facility

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the study team until the abnormal parameter or symptom has resolved or stabilized.

Subjects who are discharged from the hospital will not continue taking Maraviroc outside the hospital. Early completion prior to seven days of therapy will not be considered early withdrawal from the study. All subjects who discontinue study treatment will undergo an early discontinuation visit as soon as possible and will be encouraged to complete all remaining scheduled research labwork (except in the instance of comfort measures and hospice). Subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feel that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early should have an early discontinuation visit. Refer to Section 10 for early termination procedures.

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced. Subjects who are discharged from the hospital due to clinical improvement prior to completing the 7-day course will not be replaced. Subjects may be added to the study to replace subjects with incomplete data (said subjects will continue to receive Maraviroc) stemming from research bloodwork processing errors due to mishandling of shipments resulting in compromised fidelity of samples.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety, and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Non-compliance with study drug regimen, including dose-reduction protocol

- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator and forwarded to the IRB. Documentation of Protocol Violations will be stored on IRB.net.

14 DATA SAFETY MONITORING

Despite Maraviroc being well-tolerated without significant side effects in previous trials and its current use in patients with HIV, vigilance and at minimum daily audits of subjects' objective and subjective response to treatment is required given the aggressiveness of SARS-CoV-2. The trial team will be responsible for eliciting adverse events and reviewing inpatient documentation daily. The trial team has specifically pre-defined possible adverse events. However, given the multitude of possible adverse events, the study protocol is not able to define all of them in advance as many may not lend themselves to satisfactory definition during trial design. Adverse events will be monitored by the Investigators and Medical Monitor during the study.

14.1 POSTURAL DIZZINESS AND ORTHOSTATIC HYPOTENSION

In healthy volunteers, orthostatic hypotension four hours after administration of Maraviroc was observed in subjects receiving high doses (600mg or more) of Maraviroc versus placebo. Per package labeling, it is recommended that users who also take an anti-hypertensive medication be asked about symptoms of orthostatic hypotension. Of note, in two Phase 3 trials, 8% of patients in active (exposure adjusted rate of 14.1 per 100 pt-yrs) and placebo drug groups described postural dizziness, but the rate of discontinuation due to syncope or orthostatic hypotension between the Maraviroc group and the placebo were reported at 0.5%. Of the 840 subjects who received one dose of Maraviroc, 2 discontinued therapy (1 due to syncope, 1 due to orthostatic hypotension, with an exposure adjusted rate of .07 per 100 pt-yrs). [18] It is possible that the rate of dizziness is related to the length of therapy. In a pilot study of investigating two months of Maraviroc (300 mg BID) in 11 colorectal cancer patients with metastasis to the liver, Grade 1 dizziness was observed in 1 patient. No patient had dizziness Grade 2 or higher (exposure adjusted rate of 5.1 per 100 pt-yrs).[13]

Based on experience with the Phase 3 trial, in which both the Maraviroc group and Placebo had exposure adjusted rates of 14.1 versus 17.1, respectively, 6 to 8 patients are expected to experience postural dizziness in a cohort of 40 patients who complete 7 days of therapy. Based on a similar calculation for orthostatic hypotension, we would expect to see less than one patient experience orthostatic hypotension requiring discontinuation of therapy. We recognize that patients with SARS-CoV-2 may be pre-disposed to postural dizziness and orthostatic hypotension because of their illness and poor oral intake, and therefore;

[13] Halama N, Zoernig I, Bertel A, et a. Thumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. Cancer Cell. 2016;29(4):587-601

observed orthostasis is unlikely to be from Maraviroc given the low aforementioned incidence in Phase 3 trials. Furthermore, a study of orthostatic vital signs checked three times in one day in elderly patients admitted to the hospital (most commonly for stroke, infectious diseases, or other reasons) revealed that 2/3 of patients had one set of abnormal orthostatic vitals[14]. Therefore, we outline below dose-reduction and stop criteria per patient to address the risk for orthostasis.

Rates, severity, and relationship of postural dizziness, as well as exposure adjusted rates for orthostatic hypotension resulting in discontinuation, will be calculated at the point in which 10 patients have received more than four doses of treatment. The Medical Monitor may request trial stoppage in the instance that an unacceptable rate of discontinuation due to orthostatic hypotension reasonably attributable to Maraviroc is observed.

14.1.1 Dose reduction protocol:
All dose-reductions will be recorded in each subjects CFR.

Patients will be initiated on Maraviroc 300 mg twice daily. Orthostatic vitals will be obtained four hours after the first dose unless otherwise contra-indicated. If symptomatic and orthostatic, the next dose of Maraviroc can be held and inpatient team will be advised to review anti-hypertensive strategy, diuretic use and consider supplemental intravenous fluid if patient is anorexic and dehydrated. Subjects will be re-trialed on 300 mg of Maraviroc the next day. If still orthostatic, the patient will be re-trialed at 150 mg of Maraviroc the next day. Persistent orthostasis probably or definitely attributable (orthostasis that develops after starting Maraviroc that was not present at baseline) may prompt discontinuation of trial medicine with consideration of severity of orthostasis and after discussion with subject and inpatient care team. Withdrawing subjects will be asked to participate in a withdrawal visit as outlined above in section 10.14. Orthostatic vitals will be repeated during course of treatment at the discretion of inpatient care team.

The aforementioned dose reduction protocol will apply to subjects on a moderate or strong CY3PA4 inhibitor, who will be initiated on Maraviroc 150 mg twice daily, with the distinction that dose reduction would occur to Maraviroc 150 mg once daily. For subjects on a moderate or strong CY3PA4 inducer, the subject will be initiated at Maraviroc 600 mg twice daily. If orthostatic as described above, dose-reduction to Maraviroc 300 mg twice daily, followed by Maraviroc 150 mg twice daily will be pursued. Lastly, given the clinical context, intubated and sedated subjects in an intensive care unit will be continued on Maraviroc 300 mg twice without monitoring for postural dizziness of orthostasis. Alternative causes for hypotension in this population should be explored prior to dose reducing Maraviroc.

[14] Weiss A., Grossman E., Beloosesky Y., et al.(2002) Orthostatic hypotension in acute geriatric ward: is it a consistent finding? Arch Intern Med 162:2369–2374.

14.2 CARDIAC EVENTS

In a safety analysis of two Phase 3 trials of Maraviroc involving 840 HIV-infected subjects who received at least one dose of Maraviroc over 34 weeks, including 426 who received twice daily dosing, 1.3% of subjects had cardiovascular events. More subjects in the Maraviroc group experienced cardiovascular events than in the placebo group, but the link to the drug was unclear and symptoms occurred only in those with known cardiac disease.[20] Given that our population may higher baseline risk of cardiac events, subjects with Acute Coronary Syndrome (ACS) within 6 months of enrollment will be excluded. In addition, participants will be monitored for symptoms of cardiac ischemia, heart failure or arrythmia with further investigation driven inpatient care team. The study team does not plan to routinely check cardiac biomarkers in asymptomatic patients. The safety monitor may request trial stoppage if a grade 3 or 4 adverse cardiac event occurs in any trial participant reasonably attributable to Maraviroc.

Maraviroc does not affect the QT interval.

14.3 HEPATOTOXICITY

NIH LiverTox Database gives a likelihood score D, indicating that Maraviroc is a possible rare cause of clinically apparent liver injury. The Maraviroc label includes a warning about hepatotoxicity, based on observed systemic allergic reaction prior to development of hepatotoxicity report ed in two subjects enrolled in pre-licensure clinical trials. Both patients were women, ages 24 and 27, who developed fever, fatigue, and rash prior to liver test abnormalities within 1 to 3 weeks of starting Maraviroc. In both instances, other potential causes were present, but no other diagnosis was confirmed. For these reasons, hepatitis and hepatic failure are listed as adverse events in the product label which includes a boxed warning about hepatotoxicity. In post-marketing surveillance, one case of life-threatening hepatotoxicity, which eventually led to liver transplantation, after 4 doses of Maraviroc has been described in a patient who also received isoniazid and trimethoprim-sulfamethoxazole. In two Phase 3 trials of HIV patients on Maraviroc for an average of 34 weeks, no overall increase in ACTG-defined Grade 3 of 4 (>5 x ULN) liver function test abnormalities were observed in a clinical trial of Maraviroc in treatment-experienced subjects with HIV. [15]

Short-term use of Maraviroc may be generally well-tolerated. Short-term use of Maraviroc was not associated with hepatic intolerance in a study of 63 HIV-1 positive individuals receiving 10-day Maraviroc monotherapy. [16]

At baseline, clinical trials enrolling younger SARS-CoV-2 patients have demonstrated hepatocellular transaminitis (AST and ALT >2 x ULN) in 20-40% of patients at time of enrollment 13 days (median) from symptom onset. In clinical practice, hepatocellular transaminitis as high as 4 x ULN is frequently encountered in hospitalized patients. [4]

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[15] Selzentry (Maraviroc) [package insert] New York, NY: Pfizer Inc; 2007

[16] Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1, Nat Med, 2005, vol. 11 (pg. 1170-2)

Given the high incidence of hepatitis at baseline in SARS-CoV-2 patients, we expect to observe high incidence of low-grade liver function test abnormalities during lab monitoring. Therefore, we elect to implement Common Terminology Criteria for Adverse Events (CTCAE) v5.0, which incorporates change in liver function testing from baseline to characterize AE grade. The recommendation from the FDA labeling is to obtain liver function tests prior to starting the drug and again should symptoms such as rash occur. We will obtain both baseline and repeat liver function test should allergic symptoms such as rash occur. Liver function testing obtained per routine care will be collected daily. Exposure adjusted rates of Grade 3 or 4 changes in liver function testing resulting in discontinuation will be calculated at the point in which eight patients have received more than four doses of treatment. The Medical Monitor may request trial stoppage in the instance that an unacceptable rate of Grade 3 or 4 changes in liver function testing resulting in discontinuation reasonably attributable to Maraviroc is observed.

14.4 OTHER ADVERSE EVENTS

Additional adverse events commonly reported include fever, cough, rash, abdominal pain, and increased risk of infections including upper respiratory tract infections. Trial data was obtained from patients with HIV infection at greater risk for infection, Immune Reconstitution Syndrome (IRIS), and malignancy which may have been secondary reasons for fever. Acknowledging the anticipated frequency of fever and cough in SARS-CoV-2 patients, the study team will monitor for evidence of secondary infection.

14.5 UNANTICIPATED ADVERSE EVENTS

As the above anticipated adverse events were noted in a population which varies from our study population hospitalized adults with SARS-CoV-2 infection, it is also important to monitor for unexpected adverse events. Serious, un-anticipated adverse events including sepsis, shock, respiratory failure, or death will be closely monitored for and reported. As this is a population with a high risk of adverse outcome related to SARS-CoV-2 itself, course of infection in participants will be monitored for any deviation from the natural history of SARS-CoV-2 infection, based on available clinical trial data and clinical experience. The monitor may request trial stoppage if any unexpected grade 4 event occurs in unacceptable rate due to Maraviroc. They may also request stoppage if there is noted to be a serious adverse event temporally or otherwise clearly related to administration of the drug in any participant, and/or if there is noted to be a pattern of deviation from natural history of SARS-CoV-2 infection towards worsening symptomatology and/or increased incidence of adverse events. The monitor may request trial stoppage if any unexpected grade 4 event probably or definitely attributable to Maraviroc occurs at an unacceptable rate.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible subjects who receive at least one dose of the study drug, or who have had more than one set of serum samples available for biomarker testing will be included in the analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, height and weight, BMI, hemodialysis, cardiovascular diseases (hypertension, known valvular disease, cardiomyopathies and/or LV systolic or diastolic dysfunction), and pulmonary disease (including OSA, COPD, asthma, interstitial lung disease, cystic fibrosis, bronchiectasis, lung transplant, lung cancer, pulmonary hypertension), oxygen device and requirement at time of enrollment, oxygen saturation on ambient air at time of enrollment, and time from onset of symptoms to presentation to enrollment.

15.3 Analysis of Endpoints

Continuous data obtained will be expressed by mean ± standard deviation (SD) or interquartile range, as applicable. Categorical variables will be reported as frequency and percentages. ICU LOS (and mechanical ventilation LOS, respectively) will be regressed on available laboratory and biomarker data using multivariable linear regression. All analysis will be conducted in a professional statistical program. Mortality and percent of study population reaching clinical improvement at Day 7 will be compared to published results from Remdesivir for 5 or 10 Days in Patients with Severe COVID-19, and other available clinical trials including The Randomized Evaluation of COVID-19 therapy (RECOVERY) Trial.

15.4 Interim Analysis

Refer to Section 14 regarding interim adverse event analysis.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Data will be stored in REDCap, a HIPAA compliant data capture toolStudy personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Clinical data will be recorded using a modified WHO–International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) Rapid Version Case Record Form. Daily diary cards recording data on a seven-category ordinal scale will be captured in REDCap. Subjects will not be identified by name inREDCap, but will be identified by a subject number and initials.

If a correction is required for an eCRF, the time-and-date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

16.2 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation in REDCap. Only specimen ID will be provided to InCellDx , the Elias Lab and the Prlic Lab during sample analysis. When submitting data to a peer-review journal, only age, gender, race and pre-existing medical conditions will be disclosed for each subject.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days. Protocol amendments will be tracked on IRB.net.

17.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the Lifespan IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB unconditional approval statement will be transmitted by the Investigator to Pfizer prior to initiation of the study. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the

patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed. Updated documents will be stored on IRB.net.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The consent form generated by the Investigator must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be scanned into Epic and the original will be given to the subject.

17.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.