C O N F I D E N T I A L

CLINICAL TRIAL PROTOCOL

FEnofibRate as a Metabolic INtervention for Coronavirus Disease 2019 (COVID-19): A randomized controlled trial (FERMIN trial)

Version: V5: November 3rd, 2021

NCT04517396

Investigators, Steering Committee Members, Center Investigators, Project Manager and DSMB Members are listed in Appendix 4

Table of Contents

SUMMARY AND TRIAL OVERVIEW 3
1. BACKGROUND AND SIGNIFICANCE 4
2. STUDY DESIGN AND POPULATION 5
2.1. Overview of study design 5
2.2. Study Sites 5
2.3. Study Population 5
2.4. Screening and enrollment 6
2.6. Randomization procedure 6
2.7. Participant withdrawal / Early termination 7
2.8. Concomitant Medication 7
2.9. Drug dispensing 7
2.10. Follow-up assessments 7
3. ENDPOINTS 8
4. ADVERSE EVENTS 10
4.1. Adverse Event Reporting 10
4.2. Key definitions 10
4.3. Classification of AEs 10
4.4. Pregnancy 11
5. DATA COLLECTION 11
6. DATA SAFETY MONITORING BOARD 11
7. STATISTICAL CONSIDERATIONS 12
7.1. Power calculations 12
7.2. Data Analysis Plan 12
7.3. Subgroup analyses and effect modification 14
8. PROTECTION OF HUMAN SUBJECTS 14
8.1. Potential benefits of the proposed research, importance of the knowledge to be gained, and risk/benefit ratio 14
8.2. Risks to study subjects 14
8.3. Adequacy of Protection Against Risks 16
8.3.1. Recruitment and Informed Consent 16
8.3.2 Measures to minimize the risk of breach in confidentiality: 16
9. REGULATORY STANDARDS 17
10. ADAPTIVE DESIGN 17

SUMMARY AND TRIAL OVERVIEW

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), is associated with a high incidence of acute respiratory distress syndrome (ARDS) and death. Aging, obesity, diabetes, hypertension and other risk factors associated with abnormal lipid and carbohydrate metabolism are risk factors for death in COVID-19.
Recent studies suggest that COVID-19 progression is dependent on metabolic mechanisms. Moreover, gene expression analyses in cultured human bronchial cells infected with SARS-CoV-2 and lung tissue from patients with COVID-19, indicated a marked shift in cellular metabolism, with excessive intracellular lipid generation. In this cell culture system, fenofibrate (a widely available low-cost generic drug approved by the FDA and multiple other regulatory agencies around the world to treat dyslipidemias) at concentrations that can be achieved clinically, markedly inhibited SARS-CoV-2 viral replication. Fenofibrate also has immunomodulatory effects that may be beneficial in the setting of COVID-19. The aim of this trial is to assess the clinical impact of fenofibrate (administered for 10 days) to improve clinical outcomes in patients with COVID-19.

The **primary endpoint** of the trial will be a global rank score that ranks patient outcomes according to 5 factors: (1) time to death (ranked from shortest to longest, up to 30 days post-randomization), (2) the number of days supported by mechanical ventilation (invasive or non-invasive) or extracorporeal membrane oxygenation (until hospital discharge, up to 30 days post-randomization, ranked from longest to shortest); (3) The inspired concentration of oxygen/percent oxygen saturation (FiO_2/SpO_2**)** ratio area under the curve (until hospital discharge, up to 30 days post-randomization, ranked from highest to lowest); (4) For participants enrolled as outpatients who are subsequently hospitalized, the number of days out of the hospital during the 30 day-period following randomization (ranked from lowest to highest); (5) For participants enrolled as outpatients who don't get hospitalized during the 30-day observation period, the modified Borg dyspnea scale (mean value of assessments at ~5, and ~10 and ~15 days).

Secondary endpoints will include:
(1) Number of days alive, out of the intensive care unit, free of mechanical ventilation (invasive and non-invasive), extracorporeal membrane oxygenation (ECMO) or maximal available respiratory support in the 30 days following randomization.
(2) A seven-category ordinal scale consisting of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 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 extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or both; and 7, death.
(3) A global rank score similar to the primary endpoint, but using a more comprehensive COVID-19 symptom scale instead of the dyspnea Borg scale (Appendix 1).

Exploratory endpoints will include:
(1) All-cause death.
(2) Number of days alive and out of the hospital during the 30 days following randomization.
(3) A global rank score similar to the primary endpoint, but built only with factors 1-4.

All primary analyses will be performed on an intent-to-treat basis.

1. BACKGROUND AND SIGNIFICANCE

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), is associated with a high incidence of acute respiratory distress syndrome (ARDS) and death.[1]

Recent studies suggest that COVID-19 progression is dependent on metabolic mechanisms.[2] T2DM and hypertension have been identified as the most common comorbidities for other serious coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS-CoV).[2,3] Individuals infected with COVID-19 who developed ARDS and death have been characterized by older age and a higher prevalence of hypertension, diabetes, and cardiovascular diseases compared to those individuals with milder disease.[2,4-6] Hyperglycemia and hyperlipidemia are also risk factors for acute respiratory distress in the setting of COVID-19.[2,7] Indeed, patients with T2DM and the metabolic syndrome appear to have up to ten-times greater risk of death when they contract COVID-19.[2]

Several experimental studies suggest a mechanistic link between abnormal metabolism and the severity of SARS-CoV-2 and other coronavirus infections. Palmitoylation of SARS-CoV spike proteins has been shown to be essential for virion assembly and for partitioning into detergent-resistant membranes and for cell-cell fusion.[8] For other coronaviruses, lipid accumulation occurs upon infection.[9] Recent gene expression analyses in cultured human bronchial cells infected with SARS-CoV-2 and lung tissue from patients with COVID-19, indicated a marked shift in cellular metabolism, with excessive intracellular lipid generation.[9] Ehrlich *et al* studied the metabolic rewiring induced by SARS-CoV-2 infection in the transcriptional signature of primary bronchial epithelial cells, validating their results in lung biopsy samples of COVID-19 patients. This study reported a significant metabolic response in SARS-CoV-2 infected lungs, covering ~60% of the differentially expressed genes.[9] This transcriptional signature was characterized by changes in metabolism and pathways of endoplasmic reticulum stress, including upregulation of glycolysis and dysregulation of the citric acid cycle, upregulation of fatty acid and cholesterol synthesis, and the suppression of fatty acid oxidation. Peroxisome proliferator-activated receptor-alpha (PPARα) inhibition was shown to be in involved in abnormalities in lipid metabolism in these experiments.

In further cell culture experiments, the PPARα-agonist fenofibrate (a widely available low-cost generic drug approved by the FDA and multiple other regulatory agencies around the world to treat dyslipidemias) at concentrations that are likely to be achieved clinically, reversed the metabolic changes induced by SARS-CoV-2, and inhibited viral production/replication.[9] Treatment of SARS-CoV-2 infected cells with fenofibrate (concentration: 20 μM) blocked phospholipid accumulation and increased glycolysis, reversing the metabolic effects of infection. Viral replication was effectively blocked, reduced by 3-log over 5 days period to below the assay detection limit, while cell viability was unaffected. Fibrates also appear to exert immunomodulatory effects that could be beneficial in the setting of COVID-19.[10-12] [10,11]PPAR-α activation by fibrates has been described to beneficially influence inflammation and experimental lung injury.

Whereas these pre-clinical studies suggest that fenofibrate could directly target host metabolic pathways to minimize virus replication and possibly suppress its pathogenesis in lung tissue, a well-designed and rigorously executed randomized controlled trial is urgently needed to assess the potential efficacy and clinical benefit of fenofibrate in COVID-19. Fenofibrate is a widely-available, generic and inexpensive drug with a proven track record of safety for other indications (i.e., dyslipidemia). If effective for COVID-19, this trial could have a major public health impact.

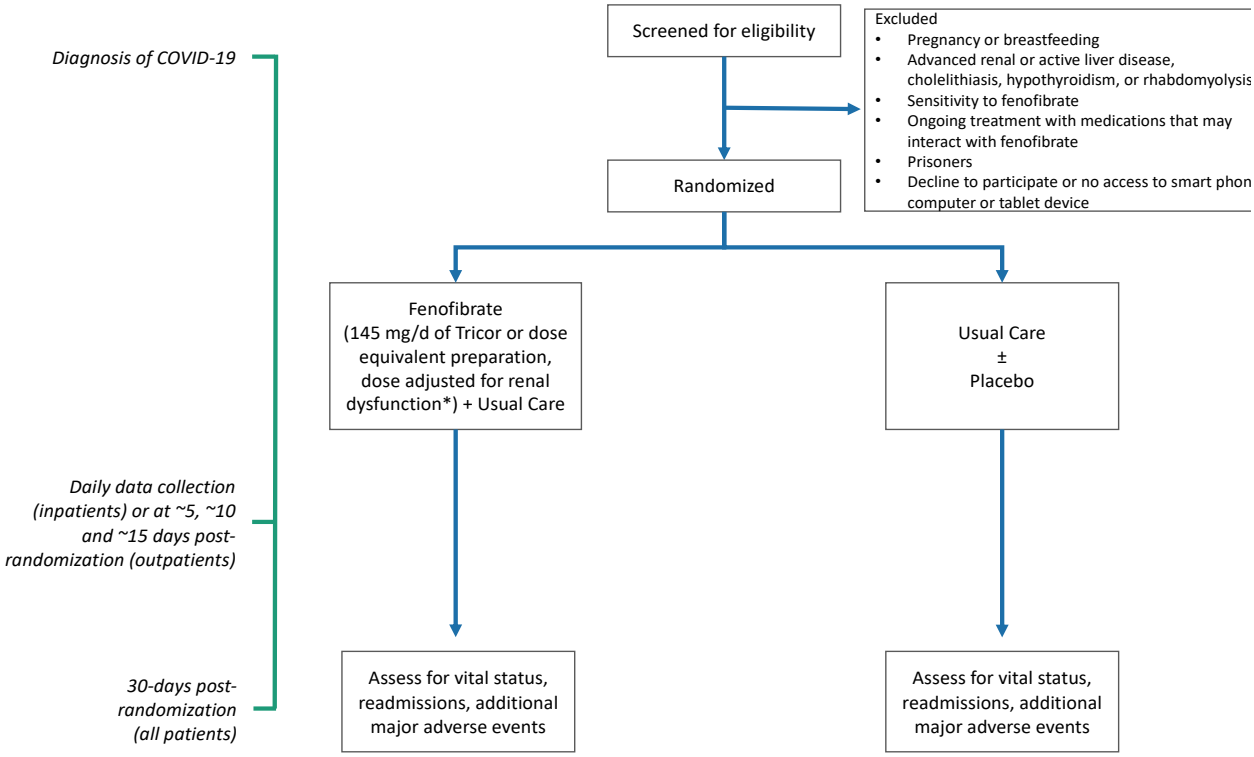
The aim of this randomized controlled trial is to assess the clinical impact of fenofibrate to improve clinical outcomes in patients with COVID-19.

2. STUDY DESIGN AND POPULATION

2.1. Overview of study design

This will be a prospective randomized controlled trial of fenofibrate therapy (administered for 10 days) among patients with COVID-19. A general overview of the trial design is shown in **Figure 1**. A schedule of events is shown in **Appendix 2**.

Figure 1. General workflow of the trial



*** According to the approved label/package insert for each particular preparation**

2.2. Study Sites

The trial will be executed at several sites in several countries, including the USA and various Latin American countries. Prior to initiation of the research in each site, IRB approval will be obtained for each site, and Health Authority approval will be obtained as per each country's regulations. In each country, there will be a qualified national PI / sponsor for regulatory processes.

2.3. Study Population

We will enroll 700 subjects meeting the following criteria:

Inclusion Criteria

(1) Age 18 years or older
(2) A diagnosis of COVID-19, based on: (a) A compatible clinical presentation with a positive laboratory test for SARS-CoV-2, or (b) Considered by the primary team to be a Person Under Investigation undergoing testing for COVID-19 with a high clinical probability, in addition to

compatible pulmonary infiltrates on chest x-ray (bilateral, interstitial or ground glass opacities) or chest CT.
(3) Able to provide informed consent.
(4) Fewer than 14 days since symptom onset.

Exclusion Criteria:
(1) Known pregnancy or breastfeeding.
(2) Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 or undergoing dialysis (CKD stages 4-5).
(3) History of active liver disease, cholelithiasis, uncontrolled hypothyroidism, or rhabdomyolysis (suspected or confirmed). Patients with a history of hypothyroidism receiving a stable dose of thyroid replacement therapy for at least 6 weeks, with a documented normal TSH (primary hypothyroidism) or free thyroxine (secondary or tertiary hypothyroidism) level at least 6 weeks after the last dose change will be considered eligible for enrollment.
(4) Known hypersensitivity to fenofibrate or fenofibric acid.
(5) Ongoing treatment with fenofibrate, clofibrate, warfarin and other coumarin anticoagulants, glimepiride, cyclosporine, tacrolimus.
(6) Use of statins other than simvastatin, pravastatin or atorvastatin ≤40 mg/d or rosuvastatin ≤20 mg/d.
(7) Prisoners/incarcerated individuals
(8) Inability to read, write or no access to a smart phone, computer or tablet device.
(9) Intubated patients.

2.4. Screening and enrollment

Patients being evaluated in the emergency room, outpatient clinics, other urgent/emergent care settings, or admitted to the hospital with COVID-19 will be screened for eligibility. We will also consider interested participants who reach out to us as a result of advertisements or other outreach efforts. Inclusion and exclusion criteria will be reviewed to ensure participant suitability. After participant eligibility is confirmed, informed consent will be obtained from study participants using documents and processes approved by the respective Institutional Review Board (IRB)/Ethics Comittee. Specific consent mechanisms and other unique aspects applied to meet regulatory requirements in a specific country are specified in **Appendix 3**. Participants will be given the opportunity to have all questions regarding their participation answered. Enrollment will be competitive (will occur across all active sites, without an enrollment cap per site) until a total of 700 patients have been recruited.

2.5. Randomized intervention

The randomized intervention will be: (1) fenofibrate (or its active metabolite, fenofibric acid) administered for 10 days (see **Appendix 3** for specific preparations and dosing), [13,14] with appropriate dose reductions or exclusions will be implemented for patients with chronic kidney disease as per the approved preparation label; (2) Placebo of similar appearance (1:1 ratio). These interventions will be added to usual care. Participants and investigators (including research team members who administer the Dyspnea Borg scale and symptoms questionnaires) will be blinded to the randomized intervention. Primary analyses will be performed on an intent-to-treat basis.

2.6. Randomization procedure

Following informed consent, participants will be randomized to one of the 2 treatment arms. A stratified blocked randomization with randomly permuted blocks will be performed based on site,

sex, age group, and inpatient vs. outpatient status, given the strong impact of these factors on outcomes in COVID-19. A sufficient number of complete blocks will be generated for each stratum so that randomized assignments are available for every eligible subject. Each block will contain an equal number of allocations to each arm.

2.7. Participant withdrawal / Early termination

Participants may voluntarily withdraw from the study at any time and for any reason. The reason for study discontinuation will be recorded on the source documents and in all such participants, we will document: (1) vital signs (inpatients only); (2) compliance with the treatment; (3) adverse effects. (4) specific reason for withdrawal if possible; (5) functional status and symptoms (including the dyspnea Borg scale).

The study medication will be discontinued if any of the following occur at any time: (1) acute kidney injury with eGFR<30 ml/m^2/min; (2) Suspected or confirmed rhabdomyolysis; (3) Red or brown urine, which may indicate myoglobinuria, unless considered by the investigator to be clearly not due to rhabdomyolysis (for instance, in the presence of normal circulating creatine kinase); (4) Liver failure or increased AST or ALT to >3 times the upper limit of normal. In cases in which the medication is discontinued, data collection will continue normally as per the usual study protocol.

2.8. Concomitant Medication

Participants will be treated by their clinicians, at their discretion, with standard of care medications for COVID-19 and associated comorbidities. Participants will be allowed to receive antiviral, immunomodulatory, or convalescent plasma. Since fenofibrate/fenofibric acid are well-known medications, enrollment in other clinical trials will be allowed as long as fenofibrate/fenofibric acid use is not an exclusion criterion for other trials.

We will remind inpatient clinicians to consider potential interactions with fenofibrate, particularly in patients who require *de novo* warfarin treatment (which should ultimately be guided by INR checks as per standard practice). We will also ask them to try avoiding the *de novo* use of medications that may interact with fenofibrate or fenofibric acid (colchicine, glimepiride, cyclosporine, tacrolimus, statins) unless clear indications exist in the absence of suitable therapeutic alternative agents; if glimepiride, cyclosporine or tacrolimus are required, we will discontinue the study medication. For colchicine, atorvastatin and simvastatin, we will ask clinicians to be mindful of a potential interaction, which is however, not anticipated to constitute a significant risk with only 10 days of treatment (see section on “Risks to study subjects”). If cholestyramine or colestipol are part of the medical regimen at baseline or during the period of study medication administration, we will ask participants to take the study medication at least 1 hour before or 6 hours after the bile acid binding resin to avoid a pharmacokinetic interaction (reduced absorption). For outpatients, we will ask participants to contact us if any new medication is initiated by their physicians during the treatment period, and we will establish a similar approach in communication with the prescribing clinician.

2.9. Drug dispensing

The drug will be dispensed by a Pharmacy within each country and/or institution, or directly by the investigators. At the University of Pennsylvania, the medication and placebo will be dispensed by the UPenn Investigational Drug Pharmacy.

2.10. Follow-up assessments

For participants randomized as inpatients, daily assessments (via medical record review) will be performed to assess clinical status, with particular attention to the study endpoints (death, mechanical ventilation and the FiO_2/SpO_2 ratio), until hospital discharge or 30 days (whichever is shortest). For participants discharged prior to 30 days-post randomization, a follow-up call will be performed at the ~30-day time point to assess vital and functional status, symptoms and major adverse events, including hospitalizations.
For participants randomized as outpatients or discharged within 24 hours of receiving the first dose of the study medication, participants will be called at approximately 5, 10, 15 and 30 days post-randomization, in order to assess vital and functional status, hospitalization status, the severity of dyspnea (via the modified Dyspnea Borg Scale, **Appendix 1**) and major adverse events. An effort will be made to make these assessments at the exact time points, but we recognize that this is often not possible due to work schedules and inability to get in touch with participants for various reasons. In these instances, we will make the assessments at time points that are as close as possible to the scheduled time points.

3. ENDPOINTS

The **primary endpoint** of the trial will be a global rank score that ranks patient outcomes according to 5 factors: (1) time to death (ranked from shortest to longest, up to 30 days post-randomization), (2) the number of days supported by mechanical ventilation (invasive or non-invasive) or extracorporeal membrane oxygenation (until hospital discharge, up to 30 days post-randomization, ranked from longest to shortest); (3) The inspired concentration of oxygen/percent oxygen saturation (FiO_2/SpO_2**)** ratio area under the curve (until hospital discharge, up to 30 days post-randomization, ranked from highest to lowest); (4) For participants enrolled as outpatients who are subsequently hospitalized, the number of days out of the hospital during the 30 day-period following randomization (ranked from lowest to highest); (5) For participants enrolled as outpatients who don't get hospitalized during the 30-day observation period, the modified Borg dyspnea scale (mean value of assessments at ~5, ~10 and ~15 days). Patients who are enrolled as inpatients but discharged within 24 hours of receiving the first dose of the study medication will be ranked similarly to outpatients.

The global rank score has several advantages compared to binary outcomes (e.g., all-cause death) or time-to-event outcomes (e.g., time to death).[15-17] It incorporates information about each of the highest-priority events in COVID-19, but allows these events to be prioritized within a single endpoint. For instance, the principal outcome of interest is death, but even if there is no difference in rate of death, we would still be interested in a shorter duration of invasive respiratory support, a shorter duration of hospital admission with better oxygenation parameters, and so on. This maximizes study power and minimizes the number of participants that need to be enrolled in order to detect clinically-meaningful differences.

Figure 2 demonstrates how participants will be ranked hierarchically according to their clinical course. All primary analyses will be performed on an intent-to-treat basis.

Secondary endpoints will include:
(1) Number of days alive, out of the intensive care unit, free of mechanical ventilation (invasive and non-invasive), extracorporeal membrane oxygenation (ECMO) or maximal available respiratory support in the 30 days following randomization.
(2) A seven-category ordinal scale consisting of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental

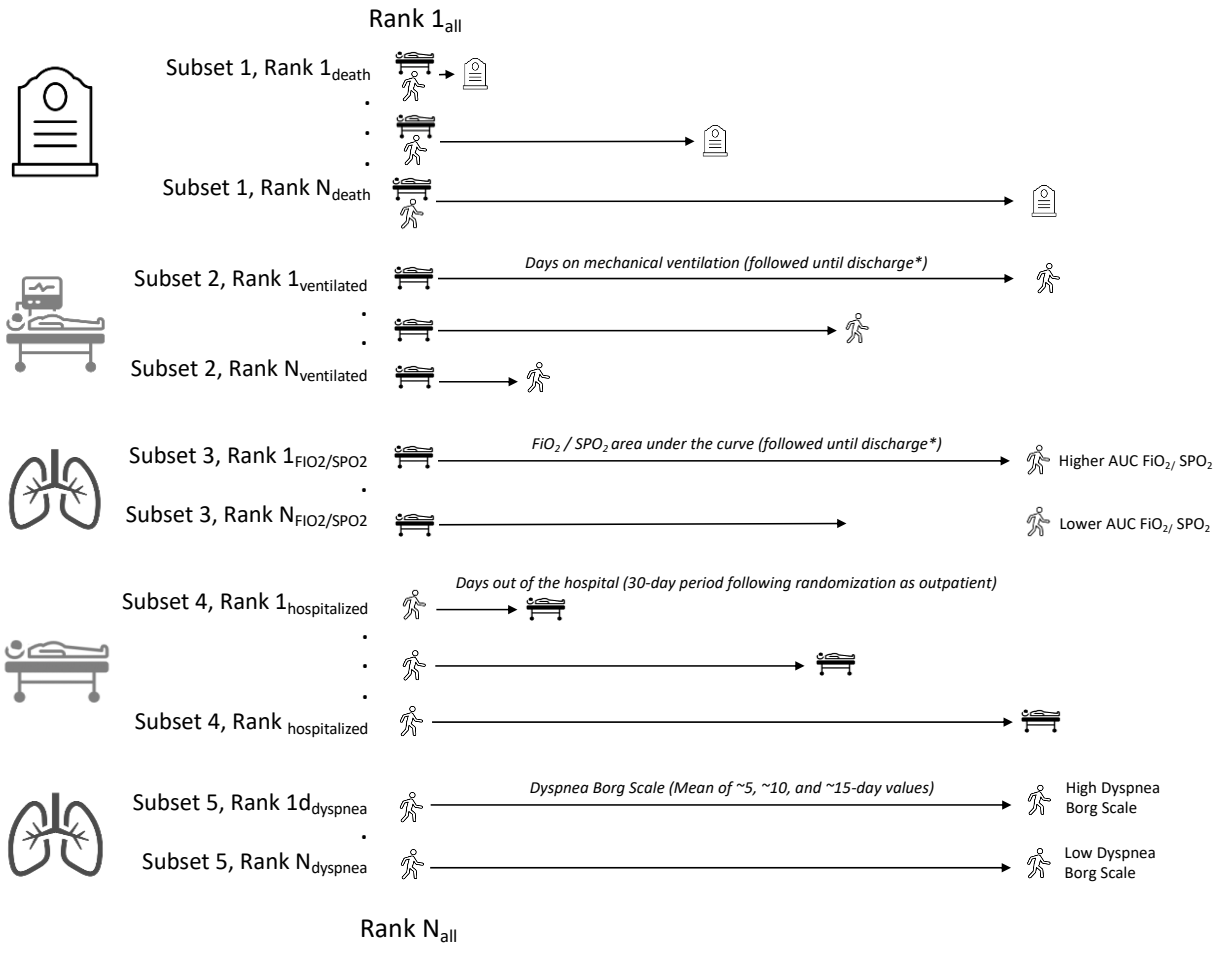
oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or both; and 7, death.

(3) A global rank score similar to the primary endpoint, but using a more comprehensive COVID-19 symptom scale instead of the dyspnea Borg scale (Appendix 1).

Exploratory endpoints will include:

(1) All-cause death.
(2) Number of days alive and out of the hospital during the 30 days following randomization.
(3) A global rank score similar to the primary endpoint, but built only with factors 1-4.

Figure 2. Hierarchial ranking for the primary endpoint



= outpatient; = inpatient.

* For participants enrolled as inpatients, inpatient mandatory data collection will occur until discharge or 30 days (whichever is shorter)

4. ADVERSE EVENTS

4.1. Adverse Event Reporting

Adverse events (AEs) will be captured in our data entry tool (RedCap). The DSMB will examine data periodically in order to compare the incidence of adverse events in both arms. Expedited reporting of individual AEs (within 48 hours or discovery by site investigators) will be required for severe AEs that are unexpected and felt to be probably or definitely associated with the study intervention. Such expedited reporting of AEs will be done from site investigators to the University of Pennsylvania study team, and the study team will in turn communicate these to the DSMB.

4.2. Key definitions

An AE is any untoward medical occurrence associated with the use of a drug in a study participant whether or not considered drug or biologic related. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the pharmaceutical product.

4.3. Classification of AEs

A medically-qualified investigator will assess AEs in terms of causal relationship to intervention, seriousness, and expectedness using the following guidelines:

Classification of Adverse Events for Causal Relationship to the Study Intervention	
Not related or unlikely related	There is not a reasonable causal relationship to the investigational product and the adverse event, or there is a low likelihood that a causal relationship exists.
Probably or definitely related	There is reasonable or definite evidence to suggest a causal relationship between the drug and adverse event.

The events will be classified as serious or non-serious adverse events:

Serious Adverse Events (SAE) are adverse events, in which the investigator or sponsor believe that any of the following outcomes occur:

- Death
- Life-threatening AE: Places the participant at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of hospitalization.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

Expectedness*:* Expected AEs will be those that are reported to be associated with COVID-19.

The following AEs are expected, disease-related events in patients with COVID-19

1. Arrhythmias, including ventricular arrhythmias and atrial fibrillation.

2. Acute coronary syndromes with or without coronary stenoses on coronary angiography
3. Myocarditis or worsening cardiac function.
4. Shortness of breath, pneumonia, acute respiratory distress syndrome and respiratory failure.
5. Fever, malaise and myalgia.
6. Worsening cognitive function.
7. Limb ischemia, coagulopathy, thrombosis, embolus.
8. Hypotension or hypertension.
9. Diarrhea, nausea, or vomiting.
10. Anosmia (loss of sense of smell).
11. Leukopenia or leukocytosis, thrombocytopenia.
12. Worsening renal function (resulting in various electrolyte abnormalities).
13. Worsening liver function.
14. Death.

4.4. Pregnancy:

Limited available data of fenofibrate use in pregnant women are insufficient to determine any association between fenofibrate and the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, no evidence of embryo-fetal toxicity was observed with oral administration of fenofibrate in rats and rabbits during organogenesis at doses less than or equivalent to the dose used in this trial, based on body surface area (mg/m^2). Known pregnancy will be an exclusion criterion for enrollment. In addition, sexually active females of reproductive age who are not receiving active contraception will undergo a pregnancy test prior to randomized drug initiation. A positive test will prompt exclusion and/or discontinuation from the study. Additional processes related to pregnancy risks may be implemented in specific countries, to meet national regulatory requirements.

5. DATA COLLECTION

The data coordinating center (DCC) will be established under the direction of Dr. Jordana Cohen. The DCC will oversee randomization, data entry, and DSMB meetings. The data for this trial will be collected in *ad hoc* source electronic case report forms. All source documents collected in this trial will be housed by the site principal investigators.

Data capture and storage will be accomplished within the framework of the Research Electronic Data Capture (REDCap) project. REDCap is a secure, web-based application designed exclusively to support data capture for research studies. It provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, including SAS and STATA, and procedures for importing data from external sources.

All electronic data at the DCC will be housed in a secure server at the University of Pennsylvania. This will allow efficient workflows regardless of location, quarantine, and social distance policies, since investigators and research staff can access these documents using existing secure VPN mechanisms.

6. DATA SAFETY MONITORING BOARD

A DSMB will be assembled to provide independent oversight of the project. The DSMB will be responsible for assessing: 1) baseline comparability between groups; 2) participant accrual rate and retention; 3) data quality with special emphasis on eligibility data; and 4) participant safety. The board will make recommendations regarding: study continuation, protocol modification, and

review of additional data. The conference call meetings and progress reports will be set by the DSMB. The DSMB will review detailed safety data according to pre-defined milestones (i.e., after 50% of participants are enrolled) which can be adapted as the trial proceeds, as per DSMB member decision.

7. STATISTICAL CONSIDERATIONS

7.1. Power calculations

We will enroll 700 participants. Participants will be randomized to one of 2 interventions (fenofibrate plus usual care vs. placebo plus usual care). Assuming feasible distributions of participants across each of the five hierarchies from the available published evidence,[4,18,19] we performed 10,000 simulations of rank distributions of 700 participants, and determined that there will be 80% power at an alpha of 0.0492 (allowing for one interim analysis at 50% of enrollment with an alpha of 0.0054[20,21]) to observe an 11% difference in median rank scores between the treatment arms. Power calculations were performed using python and PASS16.[22]

Enrollment of 700 participants will increase our power for secondary outcomes. For the secondary outcome of number of days alive, out of the intensive care unit, free of mechanical ventilation (invasive and non-invasive), extracorporeal membrane oxygenation (ECMO) or maximal available respiratory support in the 30 days following randomization, assuming a standard deviation of 7 (the SD from the REPLACE COVID trial for this outcome),[23] a sample size of 700 would have 90% power to estimate a 1.7 day mean difference between treatment arms.[24,25] Assuming that the SD may be higher in the current study with the inclusion of outpatients, we would have a sufficient power to estimate a 3.4 day mean difference between treatment arms with a SD of 14.

For the secondary outcome of the WHO ordinal scale, based on the ordinal scale distributions from the Remdesevir trial,[26] we would have 90% power to observe an OR of 1.5 for clinical improvement in the ordinal scale.[24,27] Given the expected lower severity of illness in our participants, with an adjusted reasonable distribution towards the lower end of the scale, we would have 90% power to observe an OR of 1.7.

For the exploratory outcome of all-cause death, assuming a death rate of 14% (observed in REPLACE COVID),[23] we would have sufficient statistical power to detect a HR of 1.4.[28,29] Considering the mixed inclusion of inpatients and outpatients, if the death rate is 5%, we would have sufficient statistical power to detect a HR of 1.7.

For the exploratory outcome of number of days alive and out of the hospital, assuming a standard deviation of 8 (the SD from the REPLACE COVID trial for this unpublished outcome),[23] a sample size of 700 would have 90% power to estimate a 2 day mean difference between treatment arms.[24,25] Assuming that the SD may be higher in the current study with the inclusion of outpatients, we would have a sufficient power to estimate a 3.9 day mean difference between treatment arms with a SD of 16.

7.2. Data Analysis Plan

The sample, both the baseline characteristics and the outcomes, will be explored and described using graphical techniques and summary statistics (means, medians, proportions and measures of variability) as appropriate. The initial description will consider the sample as a whole as well as by treatment arm.

The primary outcome variable will be the global rank score, as used previously in several similar randomized controlled trials to facilitate evaluation of composite outcomes of binary and continuous findings accounting for censorship for death.[15-17] The predictor of interest for all outcomes will be randomized intervention (fenofibrate vs. control), with analyses based upon the total number of randomized participants. Initial descriptive estimates of all measures will be generated for study participants by treatment group. Statistics will include estimates of central tendency, measures of variability, and derived moments of skewness and kurtosis. Analyses of distributional properties will be performed to determine if variance stabilizing or normalizing transformations should be applied. Outliers will be assessed via visual inspection of distributions and checked for accuracy. Additionally, the intervention groups will be compared using Fisher's Exact tests.

The primary and secondary outcomes will be analyzed using a two-sided Wilcoxon rank sum test. Estimation, and 95% confidence intervals, of the differences between arms will be based on the Hodges-Lehman median difference as well as the Mann-Whitney Parameter, the probability that a subject from the fenofibrate arm has a score greater or equal to that of a subject for the control.[30] This will be followed by a more comprehensive linear regression analysis allowing for assessments of the treatment effect on each continuous outcome of interest while controlling for effects of covariates including age, sex, inpatient vs. outpatient status at enrollment, FiO_2/SpO_2 at the time of enrollment, ethnicity, body mass index, altitude above sea level and history of diabetes at baseline.

For non-normal distributed continuous outcomes, we will utilize non-parametric methods or consider distribution-stabilizing transformations. Levine's tests will be used to assess homogeneity of variance. The models will include data from dropouts.[31-33] Model assumptions will be examined (eg, QQ plots to assess normally distributed residuals for valid Wald tests).

All-cause death will be evaluated using Cox proportional hazards models. The proportional hazards assumption will be assessed via weighted versions of Kaplan–Meier curves, using log–log plots and graphical displays based on the Schoenfeld and scaled Schoenfeld residuals, and violations of the proportional hazards assumption will be addressed with a time-interaction term.[34]

We will make every possible effort to minimize missing data and ensure final assessments for participants opting to discontinue study participation. Missing data, however, is an inevitable problem in a longitudinal study. The mechanism for missingness-missing completely at random (MCAR), missing at random (MAR), nonignorable or not missing at random (NMAR)-will be evaluated prior to implementing methodology intended to minimize bias from missing data.[35] We anticipate that <5% of randomized subjects will have missing data in the components required to compute the study outcomes. Imputation procedures will be applied as needed for missing data, and the primary analyses will use the imputed data.[36]

The intent-to-treat principle of including all randomized participants in the outcome models will be followed. Analytic methods described above will take advantage of all available data. Sensitivity analyses will be performed including only participants with laboratory confirmation of COVID-19 and using an 'as-treated' analysis. The 'as-treated' analysis will take into account subjects in the control arm who begin fenofibrate as part of their clinical care, and those in the fenofibrate arm who stop using fenofibrate for any reason. We will also perform sensitivity analyses in which the FiO_2/SpO_2 ratio will be theoretically normalized for altitude above sea level (athmospheric pressure).

Sequential monitoring and early stopping: Incidence rates of outcomes will be monitored throughout the trial and used for an interim analysis of efficacy and futility at 50% of enrollment. Group sequential methods for event rates will be used to control the Type I error to be 0.05 across repeated analyses. Critical values for interim testing will be defined based on an O'Brien-Fleming type bound (alpha 0.0052).[21] With this approach, the interim test is conservative and the reduction in the overall power of the trial caused by interim testing is small. If needed, conditional power calculations will be used to assess the futility of continuation in the presence of a negative treatment effect. The DSMB will review data on adverse events and other safety issues to make an overall recommendation concerning the safety of continuing the trial.

7.3. Subgroup analyses and effect modification

We will assess for effect modification and exploratory subgroup analyses will be performed according to sex, age (categorized by < or ≥ the median value in the study population), race, presence of pre-existing diabetes, body mass index (categorized by obese or non-obese), inpatient vs. outpatient status at the time of enrollment, FiO_2/SpO_2 at the time of enrollment (categorized by < or ≥ the median value in the study population), duration of symptoms prior to randomization (<7d vs. ≥7 days) and fasting triglyceride levels (when available, categorized by < or ≥ the standard median value).

8. PROTECTION OF HUMAN SUBJECTS

8.1. Potential benefits of the proposed research, importance of the knowledge to be gained, and risk/benefit ratio

Potential benefits: There are no known direct benefits to the subjects as a result of their participation in this study nor will this be implied when obtaining consent.

Potential risks: please refer to section 8.2

Importance of the knowledge to be gained: Our study will address a highly important clinical question that may impact the care of a large number of patients affected by the COVID-19 pandemic. This study will provide randomized trial evidence about the impact of a wide available, generic and inexpensive drug with a proven track record of safety for other indications (i.e., dyslipidemia). However, it is essential to rigorously and promptly study its potential clinical efficacy in a randomized controlled trial.

Risk/benefit ratio: given the importance of knowledge to be gained and the proven track record of safety of this medication, the risk/benefit ratio of our trial is favorable.

8.2. Risks to study subjects

All subjects will be adults able to give informed consent. Subjects will be enrolled regardless of sex, race or ethnicity, aiming to assure adequate representation of women and ethnic minorities. Children will not be enrolled.

The risks to study subjects are related to the potential side effects of the study intervention. The dose used in this trial is the starting dose for primary hypercholesterolemia and mixed dyslipidemia[14] and is utilized as a chronic therapy, for months or years. We propose to administer this dose for only 10 days.

With chronic therapy, adverse reactions > 2% and at least 1% greater than placebo include abnormal liver blood tests (increased AST and ALT) increased creatine kinase (CPK), and rhinitis. Rhabdomyolysis have been reported in patients taking fenofibrate, but is considered extremely

rare,[37-39] with <20 cases reported worldwide for fibrate monotherapy. Moreover, the median duration of therapy prior to rhabdomyolysis was 17.5 days.[39] In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, 9,795 were randomized to fenofibrate or placebo for 5 years. This provided >8 million patient-days of observation in the active arm alone. In this trial, only 3 patients allocated to fenofibrate had rhabdomyolysis, which in each case fully resolved; this incidence was not significantly different than that of the placebo arm (1 case of rhabdomyolysis).[40] The risk of rhabdomyolysis may be increased during co-administration with a statin, in renal failure, or hypothyroidism. Accordingly, we will exclude all patients with advanced renal dysfunction and those with a history of hypothyroidism.

Regarding statins, although there is an increase in reports of rhabdomyolysis with statin-fibrate combined therapy, this risk appears to be much higher when statins are combined with gemfibrozil than fenofibrate.[41] In a meta-analysis of 6 trials including 1,628 subjects taking fenofibrate in combination with statin therapy, no case of myopathy or rhabdomyolysis was reported. [42] This included data from the LCP-AtorFen trial, in which atorvastatin (40 mg/d) was administered alone or with fenofibrate for 12 weeks,[43] as well as some studies with simvastatin (20 mg/d).

The negligible risk of rhabdomyolysis with combination therapy has been repeatedly confirmed in subsequent studies. In the SAFARI trial (in which 411 patients received simvastatin 20 mg plus fenofibrate 160 mg/day) for 12 weeks, no cases of rhabdomyolysis were seen. In the FIELD trial of fenofibrate vs. placebo, no cases of rhabdomyolysis were seen among patients taking statin therapy. Finally, in the large ACCORD lipid trial,[44] in which 5,518 patients with type 2 diabetes who were already being treated with simvastatin were assigned to receive either fenofibrate (160 mg) or placebo and followed for a mean of 4.7 years (representing ~12,995 patient-years of observation or ~4.7 M patient-days, in the fenofibrate+simvastatin arm alone), no increased risk of rhabdomyolysis was seen. In this trial, the administered simvastatin dose was up to 40 mg/d. The authors concluded that this is compatible with evidence that fenofibrate, in contrast to gemfibrozil, does not increase plasma concentrations of statins.[45] Clinical data in large numbers of patients are also available for pravastatin[46] and rosuvastatin.[47] The lack of significant increase in concentrations of statins induced by fenofibrate has been shown specifically for simvastatin,[45] pravastatin[48,49] atorvastatin[50,51] and rosuvastatin.[52,53] For pravastatin, fenofibrate may slightly increase the AUC for its metabolite 3-alpha-hydroxy-iso-pravastatin, which is not considered clinically concerning given its much lower potency and lack of toxicity compared to the parent drug[48]; moreover, subsequent careful studies with dosing of up to 15 days showed no increased AUC for pravastatin or its metabolite 3alpha-hydroxy-iso-pravastatin.[49] The lack of clinically significant interactions with these statins is a clear difference with gemfibrozil, which unlike fenofibrate, does increase the AUC of atorvastatin, simvastatin, and multiple other statins.[50,54-56] There is, however, an increased AUC for pravastatin and fluvastatin[14] and there is much less data for newer statins. Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates co-administered with colchicine. A Pubmed search of “colchicine AND fenofibrate” (search performed on August 10th, 2020) returned 11 articles, of which only one was a report of a case of myopathy in patient receiving these drugs, which actually worsened upon discontinuation of fenofibrate and was ultimately proven to be due to inflammatory/autoimmune myopathy (based on biopsy data) and associated with multisystemic autoimmune disease.[57] In contrast, we found a reported case with co-administration of colchicine and gemfibrozil[58] and one with bezafibrate[59], both of which resolved upon discontinuation of the medications. Therefore, this does not appear to be a significant problem with fenofibrate and in fact, fenofibrate has been suggested as a treatment for gout, a patient population in which colchicine is very common.[60-65]

Given that we will only administer 10 days of therapy, we consider the risk of rhabdomyolysis, even in patients taking statins or colchicine, to be negligible. Nevertheless, as a precaution, we will exclude patients who are taking statins other than simvastatin and atorvastatin; similarly, we will exclude patients who are taking simvastatin or atorvastatin at doses >40 mg/d,

since doses >40 mg/d of these 2 drugs in combination with fenofibrate have not been specifically studied. Finally, we will ask site investigators to communicate any occurrence of rhabdomyolysis to the Principal Investigator, who in turn will immediately communicate them to the DSMB for a formal assessment (with unblinding of the DSMB if required). We will inquire about potential manifestations of rhabdomyolysis (particularly hemoglobinuria) in all data collection forms and the study medication will be discontinued immediately upon suspected or confirmed rhabdomyolysis.

Fenofibrate can increase serum transaminases and/or serum creatinine and periodic monitoring is recommended during chronic therapy. However, we will only utilize it for 10 days in this trial and will exclude patients with active liver disease or advanced renal disease. Therefore, the need for periodic monitoring does not apply for such as short treatment. Moreover, the mild increase in serum creatinine is not thought to be due to impaired true glomerular function, as measured by inulin clearance, the gold standard measure of renal function. This creatinine rise does not increase the risk of adverse renal outcomes or cardiovascular events, and is fully reversible upon discontinuation.[66]

Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. This is not anticipated to be a problem with 10 days of therapy, and our trial will exclude patients with a history of gallbladder disease. As recommended by the approved prescribing information, we will also exclude nursing mothers, and patients with known hypersensitivity to fenofibrate or fenofibric acid.

Fenofibrate can also rarely cause allergic reactions and mild to moderate changes in blood cell counts. Pancreatitis has been observed (in post-marketing case reports) in people taking fenofibrate for dyslipidemia, but is an extremely rare occurrence. Of note, the overwhelming majority of these reports involved patients who had other, more strongly associated risk factors for acute pancreatitis and it is unclear whether and to what degree was fenofibrate causally involved.[67,68] Moreover, the incidence of pancreatitis has been estimated to be very low (0.13 per 100 patient years on monotherapy and 0.16 per 100 patient years in combination with a statin) and such a complication is extremely unlikely with 10 days of therapy.[68]

Drugs that exhibit significant interactions with fenofibrate include coumarin anticoagulants, immunosuppresants and glimepiride. We will exclude patients taking these medications.

8.3. Adequacy of Protection Against Risks

8.3.1. Recruitment and Informed Consent:

Electronic informed consent will be obtained from the subjects or their authorized representatives prior to entry into the research study. Potential subjects will receive the IRB approved informed consent form in person or electronically to minimize risk of exposure to SARS-CoV-2. The principal investigator or sub-investigators will conduct the informed consent process in person, or via phone or video conferencing, which maximizes the efficiency of workflow and minimizes exposure of the research staff to SARS-CoV-2. When a physical ICF is utilized, for safety reasons, the copy of the physical ICF will not be retrieved from the patient's room or hospital area, and only a photograph of the signed page of the informed consent form will be kept in the electronic regulatory files.

The study intervention and potential associated risks will be explained to study subjects and they will have adequate time to ask questions. No study interventions will be initiated until the study team receives either the signed informed consent form or attestation documenting the subjects' agreement to participate.

8.3.2 Measures to minimize the risk of breach in confidentiality: All records will be treated with strict confidentiality according to guidelines and regulations related to Sensitive Patient Health Information in respective countries. Our eCRFs will be contained in secure servers at the University of Pennsylvania. A secure database of patient information will be maintained. All

documents for this trial will be electronic, but any unanticipated paper files that contain protected health information will be saved under lock in a secure area.

9. REGULATORY STANDARDS

The study will be submitted to the site's IRB/EC for approval. During the study, any amendment or modification to the protocol will be sent to the IRB/EC. Protocol deviations will be handled according to Institutional guidelines. In each country, the National Principal Investigator will lead and hold responsibility for federal regulatory processes. All site PIs will be responsible for obtaining IRB/research ethics committee approval from their respective boards and to comply with their national and institutional regulations.

10. ADAPTIVE DESIGN

The trial, including any interim safety and efficacy analyses, will be monitored by an independent DSMB. The DSMB will have the capacity to recommend termination of enrollment based on new available evidence of interim data analyses, as detailed in our DSMB charter. If the trial is terminated prematurely for any reason, follow-up will continue for all randomized participants.
An increase in the sample size will be considered depending on feasibility and pace of enrollment, to enhance the power of the study for secondary endpoints. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated. Any modification to the protocol will require approval by applicable institutional review boards/Ethics committees at enrollment sites, as well as applicable regulatory agencies in each enrollment country.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020.
2. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol.* 2020;16(6):297-298.
3. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med.* 2006;23(6):623-628.
4. 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. *The Lancet.* 2020.
5. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine.* 2020.
6. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.
7. Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab.* 2020;31(6):1068-1077 e1063.
8. McBride CE, Machamer CE. Palmitoylation of SARS-CoV S protein is necessary for partitioning into detergent-resistant membranes and cell-cell fusion but not interaction with M protein. *Virology.* 2010;405(1):139-148.
9. Ehrlich E, Uhl S, Ioannidis K, Hofree M, tenOever B, Nahmias Y. The SARS-CoV-2 Transcriptional Metabolic Signature in Lung Epithelium. *Cell Sneak Peak (submission only).* 2020.
10. Schaefer MB, Pose A, Ott J, et al. Peroxisome proliferator-activated receptor-alpha reduces inflammation and vascular leakage in a murine model of acute lung injury. *Eur Respir J.* 2008;32(5):1344-1353.
11. Hecker M, Behnk A, Morty RE, et al. PPAR-alpha activation reduced LPS-induced inflammation in alveolar epithelial cells. *Exp Lung Res.* 2015;41(7):393-403.
12. Huang D, Zhao Q, Liu H, Guo Y, Xu H. PPAR-alpha Agonist WY-14643 Inhibits LPS-Induced Inflammation in Synovial Fibroblasts via NF-kB Pathway. *J Mol Neurosci.* 2016;59(4):544-553.
13. Ling H, Luoma JT, Hilleman D. A Review of Currently Available Fenofibrate and Fenofibric Acid Formulations. *Cardiol Res.* 2013;4(2):47-55.
14. Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. *Am J Med.* 2014;127(8):717-727 e712.
15. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular Outcomes With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure: The CAT-HF Trial. *Journal of the American College of Cardiology.* 2017;69(12):1577-1587.
16. Margulies KB, Hernandez AF, Redfield MM, et al. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA.* 2016;316(5):500-508.
17. Felker GM, Maisel AS. A global rank end point for clinical trials in acute heart failure. *Circ Heart Fail.* 2010;3(5):643-646.
18. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020.
19. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5:13.

20. Julious SA. Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data. *Statistics in medicine.* 2004;23:1921-1986.
21. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35(3):549-556.
22. PASS 16 Power Analysis and Sample Size Software. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. 2018.
23. Cohen JB, Hanff TC, Corrales-Medina V, et al. Randomized elimination and prolongation of ACE inhibitors and ARBs in coronavirus 2019 (REPLACE COVID) Trial Protocol. *J Clin Hypertens (Greenwich).* 2020;22(10):1780-1788.
24. Julious SA. *Sample Sizes for Clinical Trials.* Boca Raton, FL: Chapman & Hall/CRC; 2010.
25. Chow SC, Shao J, Wang H. *Sample Size Calculations in Clinical Research.* 2nd Edition ed. New York: Dekker; 2008.
26. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *The New England journal of medicine.* 2020;383(19):1813-1826.
27. Whitehead J. Sample size calculations for ordered categorical data. *Statistics in medicine.* 1993;12(24):2257-2271.
28. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. *Control Clin Trials.* 2000;21(6):552-560.
29. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics.* 1983;39(2):499-503.
30. Fay MP, Malinovsky Y. Confidence intervals of the Mann-Whitney parameter that are compatible with the Wilcoxon-Mann-Whitney test. *Statistics in medicine.* 2018;37(27):3991-4006.
31. Willan AR, Pater JL. Carryover and the two-period crossover clinical trial. *Biometrics.* 1986;42(3):593-599.
32. Brown BW, Jr. The crossover experiment for clinical trials. *Biometrics.* 1980;36(1):69-79.
33. Grizzle JE. The Two-Period Change-over Design an Its Use in Clinical Trials. *Biometrics.* 1965;21:467-480.
34. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. In: *Statistics for Biology and Health.* New York, NY: Springer; 2001.
35. Little RJ. Modeling the drop-out mechanism in repeated-measures studies. *Journal of the American Statistical Association.* 1995;90:1112-1121.
36. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. *JAMA.* 2015;314(18):1966-1967.
37. Tahmaz M, Kumbasar B, Ergen K, Ure U, Karatemiz G, Kazancioglu R. Acute renal failure secondary to fenofibrate monotherapy-induced rhabdomyolysis. *Ren Fail.* 2007;29(7):927-930.
38. Ghosh B, Sengupta S, Bhattacharjee B, Majumder A, Sarkar SB. Fenofibrate-induced myopathy. *Neurol India.* 2004;52(2):268-269.
39. Zhou J, Li D, Cheng Q. Fenofibrate monotherapy-induced rhabdomyolysis in a patient with post-pancreatitis diabetes mellitus: A rare case report and a review of the literature. *Medicine (Baltimore).* 2020;99(21):e20390.
40. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *The Lancet.* 2005;366(9500):1849-1861.
41. Davidson MH. Reducing residual risk for patients on statin therapy: the potential role of combination therapy. *Am J Cardiol.* 2005;96(9A):3K-13K; discussion 34K-35K.
42. Guo J, Meng F, Ma N, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. *Am J Cardiol.* 2012;110(9):1296-1301.
43. Davidson MH, Rooney MW, Drucker J, et al. Efficacy and tolerability of

atorvastatin/fenofibrate fixed-dose combination tablet compared with atorvastatin and fenofibrate monotherapies in patients with dyslipidemia: a 12-week, multicenter, double-blind, randomized, parallel-group study. *Clin Ther.* 2009;31(12):2824-2838.
44. Group AS, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010;362(17):1563-1574.
45. Bergman AJ, Murphy G, Burke J, et al. Simvastatin does not have a clinically significant pharmacokinetic interaction with fenofibrate in humans. *J Clin Pharmacol.* 2004;44(9):1054-1062.
46. Farnier M. Pravastatin and fenofibrate in combination (Pravafenix((R))) for the treatment of high-risk patients with mixed hyperlipidemia. *Expert Rev Cardiovasc Ther.* 2012;10(5):565-575.
47. Strain JD, Farver DK, Clem JR. A review on the rationale and clinical use of concomitant rosuvastatin and fenofibrate/fenofibric acid therapy. *Clin Pharmacol.* 2010;2:95-104.
48. Pan WJ, Gustavson LE, Achari R, et al. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol.* 2000;40(3):316-323.
49. Gustavson LE, Schweitzer SM, Koehne-Voss S, et al. The effects of multiple doses of fenofibrate on the pharmacokinetics of pravastatin and its 3alpha-hydroxy isomeric metabolite. *J Clin Pharmacol.* 2005;45(8):947-953.
50. Whitfield LR, Porcari AR, Alvey C, Abel R, Bullen W, Hartman D. Effect of gemfibrozil and fenofibrate on the pharmacokinetics of atorvastatin. *J Clin Pharmacol.* 2011;51(3):378-388.
51. Patino-Rodriguez O, Martinez-Medina RM, Torres-Roque I, et al. Absence of a significant pharmacokinetic interaction between atorvastatin and fenofibrate: a randomized, crossover, study of a fixed-dose formulation in healthy Mexican subjects. *Front Pharmacol.* 2015;6:4.
52. Martin PD, Dane AL, Schneck DW, Warwick MJ. An open-label, randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. *Clin Ther.* 2003;25(2):459-471.
53. Zhu T, Awni WM, Hosmane B, et al. ABT-335, the choline salt of fenofibric acid, does not have a clinically significant pharmacokinetic interaction with rosuvastatin in humans. *J Clin Pharmacol.* 2009;49(1):63-71.
54. Backman JT, Kyrklund C, Kivisto KT, Wang JS, Neuvonen PJ. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther.* 2000;68(2):122-129.
55. Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ. Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther.* 2003;73(6):538-544.
56. Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther.* 2004;75(5):455-463.
57. Guiomar V, Oliveira D, Correia C, Pereira E. Efficacy of Rituximab in Refractory Inflammatory Myopathy Associated With Coexistence of Behcet's Disease and Antiphospholipid Syndrome. *Eur J Case Rep Intern Med.* 2019;6(11):001294.
58. Atmaca H, Sayarlioglu H, Kulah E, Demircan N, Akpolat T. Rhabdomyolysis associated with gemfibrozil-colchicine therapy. *Ann Pharmacother.* 2002;36(11):1719-1721.
59. Sugie M, Kuriki A, Arai D, Ichikawa H, Kawamura M. [A case report of acute neuromyopathy induced by concomitant use of colchicine and bezafibrate]. *No To Shinkei.* 2005;57(9):785-790.
60. Feher MD, Hepburn AL, Hogarth MB, Ball SG, Kaye SA. Fenofibrate enhances urate reduction in men treated with allopurinol for hyperuricaemia and gout. *Rheumatology*

(Oxford). 2003;42(2):321-325.
61. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs.* 2004;64(21):2399-2416.
62. Lee YH, Lee CH, Lee J. Effect of fenofibrate in combination with urate lowering agents in patients with gout. *Korean J Intern Med.* 2006;21(2):89-93.
63. Jung JY, Choi Y, Suh CH, Yoon D, Kim HA. Effect of fenofibrate on uric acid level in patients with gout. *Sci Rep.* 2018;8(1):16767.
64. Khanna PP. Gout: a patrician malady no more. *Lancet Diabetes Endocrinol.* 2018;6(4):263-264.
65. Waldman B, Ansquer JC, Sullivan DR, et al. Effect of fenofibrate on uric acid and gout in type 2 diabetes: a post-hoc analysis of the randomised, controlled FIELD study. *Lancet Diabetes Endocrinol.* 2018;6(4):310-318.
66. Ting R-D, Keech A. Fenofibrate and renal disease: clinical effects in diabetes. *Clinical Lipidology.* 2013;8(6):669-680.
67. McDonald KB, Garber BG, Perreault MM. Pancreatitis associated with simvastatin plus fenofibrate. *Ann Pharmacother.* 2002;36(2):275-279.
68. Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol.* 2010;106(11):1594-1601.

APPENDIX 1. DYSPNEA BORG SCALE AND COVID-19 SYMPTOM SCALE

"This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you with your usual activities today?"

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

COVID-19 Symptom scale

Rate each of the following symptoms from 0-10 (scale similar to the one above)

- Fever or Chills
- Cough
- Muscle or body aches
- Sore throat
- Loss of smell or taste
- Headache
- Diarrhea
- Fatigue
- Nausea or vomiting
- Chest pain or discomfort

All scores for individual symptoms (including dyspnea, as per the dyspnea Borg scale) are added to compute the final score.

APPENDIX 2. SCHEDULE OF EVENTS

	At Enrollment	*Daily During admission*	*~5 days post-enrollment*	*~10 days post-enrollment*	*~15 days post-enrollment*	*~30 days post-enrollment*
All participants						
Screening for Inclusion eCRF	X					
Informed Consent	X					
Randomization	X					
Baseline Medical Information eCRF	X					
Inpatients						
Daily Inpatient Information eCRF		X				
Follow-up call eCRF						X
Outpatients						
Follow-up call eCRF			X	X	X	X

Adverse Event Forms, deviation event logs and withdrawal forms will be filled at any time during the study, as needed.

APPENDIX 3. COUNTRY-SPECIFIC FENOFIBRATE PREPARATION, INFORMED CONSENT MECHANISM AND REGULATORY ISSUES

NOTE: This appendix varies in each country according to various factors in each country, including the fenofibrate preparation utilized and applicable regulatory requirements in a given country. Only information about the preparation that applies to each country will be submitted for review and regulatory approval in the respective country.

UNITED STATES:

Fenofibrate preparation and dosing

In the US, the drug and placebo will be prepared (encapsulated) by the Penn Investigational Drug Pharmacy. It will be shipped to IDS services in other enrollment sites. Administration will be double-blinded (Investigators and patient).

We will utilize Tricor tablets. The dose will be 145 mg/day with appropriate dose correction for patients with chronic kidney disease (CKD). The daily dose of Tricor for patients with CKD stage 2 will be 96 mg/d and the dose for CKD stage 3 will be 48 mg/d. In all cases, the intended duration of randomized treatment will be for 10 days.

The medication will be administered by mouth regardless of meals; in patients who are intubated, we will administer the crushed tablet (or placebo) via nasogastric tube. The latter procedure requires opening the capsule and therefore unblinds the administering nurse, which is acceptable, since in that setting (once the patient is intubated), subjective endpoints do not influence the study primary (only time to death and days of mechanical ventilation do, in tiers 1 and 2). The same is true for all secondary outcomes. Moreover, the patient and investigator will remain blinded. We have considered the alternative of preparing a blinded solution of active medication vs. placebo by IDS to be sent to the floor for administration via NG tube; however, we lack reliable data regarding the stability of the medication in solution at ambient temperature for various periods of time. Therefore, we have opted against this option.

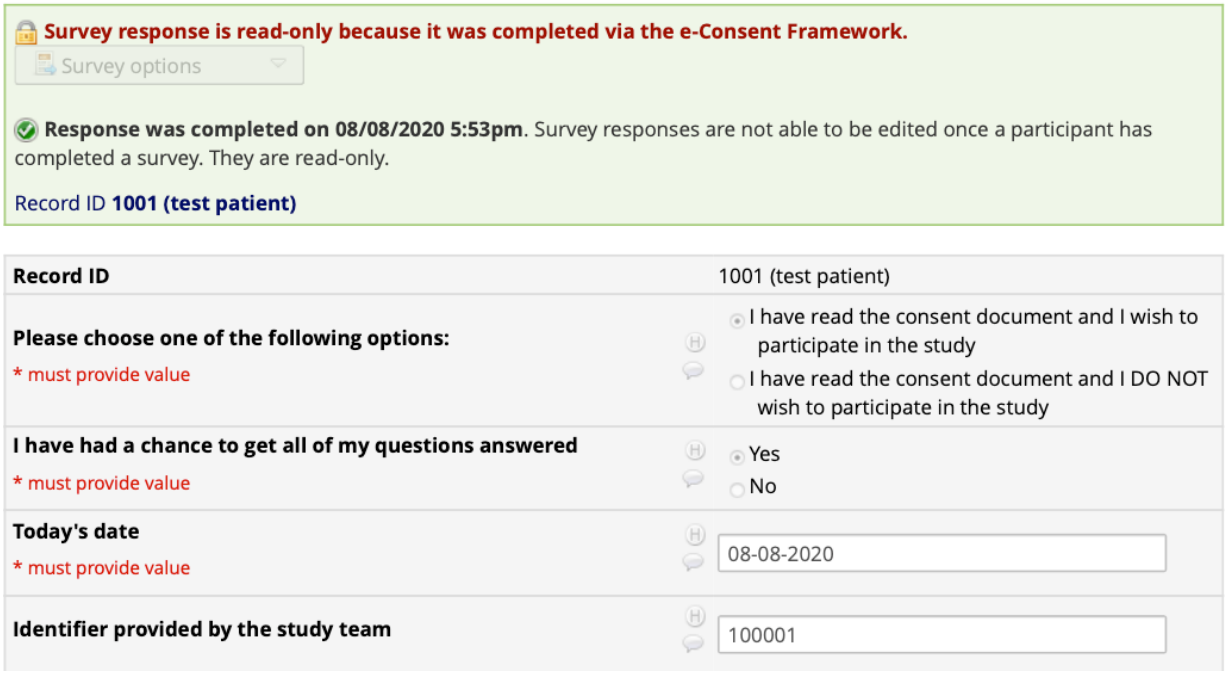
Baseline evaluation

In addition to documentation of SARSCoV infection, baseline laboratory test should include at a mininum, a creatinine level for assessment of eGFR (to determine the appropriate medication dose). These are done routinely as part of clinical care at Penn (Emergency room visits or inpatient assessments). We will also consider outpatients who reach out to us as a result of advertisements. If these participants have already had these tests elsewhere (i.e., other medical facilities), we will accept documentation of such tests. Otherwise, we will invite outpatient patients to the Center for Human Phenomics Sciences to undergo any necessary tests as per protocol.

Consent mechanism

To avoid exposure of the research team, we will perform verbal consent of study subjects. Potentially interested participants will receive an electronic version (in PDF format) of the combined ICF/HIPAA authorization form via email or other method of their choice. After they have had an opportunity to read it, we will finalize the consent process over the phone, including an opportunity to clear any doubts/questions about the protocol. At that point, if patients decide to participate, we will invite a witness to record the verbal consent. The study team will document the consent process in writing. Participants will also fill a brief RedCap survey (using their unique 4-digit ID provided by the team) further documenting their consent. An example is shown below. Alternatively, patients may print the consent form at home, sign it and send us a digital photograph

of the last page. The latter mechanism will likely be used predominantly for outpatients. Consent by legally authorized patient representatives will be allowed.



APPENDIX 4. Investigators, Steering Committee Members, Center Investigators, Project Manager and DSMB Members

National Principal Investigators
(to be modified with trial progress as needed, without the need for IRB review)

Julio A. Chirinos, MD, PhD (National PI, USA; U. of Pennsylvania)
Mario Cornejo Giraldo, MD (National PI, Perú; U. Católica de Santa María, Arequipa, Perú)
Patricio López-Jaramillo, MD (Investigador Principal Nacional, Colombia. U. de Santander; Bucaramanga, Colombia)
Dr. Jaime Andrade Villanueva (National PI Universidad de Guadalajara, Méjico)
Evangelos Giamarellos, MD, PhD (National PI, Greece; Attikon University Hospital, Athens, Greece)

Steering Committee Members
(to be modified with trial progress as needed, without the need for IRB review)

Julio A. Chirinos, MD, PhD (U. of Pennsylvania, Chair)
Jordana Cohen, MD, MSCE (U. of Pennsylvania)
Nancy Sweitzer (University of Arizona)
Juan Ortega Legaspi (U. of Pennsylvania)
Patricio López-Jaramillo, MD (Universidad de Santander, Colombia. National PI, Colombia)
Gonzalo Dávila Del Carpio, DSc (Universidad Católica de Santa María, Arequipa, Perú)
Mario P. Cornejo Giraldo, MD (EsSalud, Arequipa, Perú)
Nelson Ramiro Rosado Santander, MD (EsSalud, Arequipa, Perú)
Dr. Jaime Andrade Villanueva (Universidad de Guadalajara, Méjico)
Juan Rodriguez Mori (EsSalud, Lima; Perú)
Carola Medina (EsSalud; Lima; Perú)
Maria Cruz Saldarriaga (EsSalud; Cusco, Perú)
Rosa Cotrina Pereyra (EsSalud, Lima; Perú)
Evangelos Giamarellos, MD, PhD (Attikon University Hospital, Greece)

Data Coordinating Center:

Jordana Cohen, MD, MSCE
Jesse Chittams, MSc

Center Principal Investigators (A file with a list of Study Center PIs in each country will be kept separately)

Project Manager (UPenn): Sharkoski, Tiffany

Data Safety Monitoring Board:

John Younger, MD
Salim Virani, MD
Michael Campos, MD
Todd A. Miano, PharmD, PhD

Version Control (Summary of Changes)

V2 (August 15th, 2020):

- Fixed typo, in which one component of the primary endpoint (FiO_2/SpO_2 ratio area under the curve) was incorrectly specified to be ranked from lowest to highest (the correct ranking is from highest to lowest).
- Fixed some typos throughout.
- Eliminated possible open label administration.
- Deleted mention of interim analysis at 75% enrollment (only one interim analysis, at 50% enrollment, is planned).
- Added mention of possibility of consent by the subject's authorized representative.
- Corrected time points in Figure 2 according to protocol text.
- Added sensitivity analysis with normalization for effect of athmospheric pressure on FiO_2 above sea level.
- In order to have a universal main protocol while facilitating regulatory review/approval for countries outside the US, we have:
    - Eliminated specific mention to the preparation that will be used in the main protocol, and have placed it in Appendix 3 (Fenofibrate prescribing information).
    - We have also specified the consent process specific to the US in Appendix 3.
    - Other country-specific regulatory requirements (particularly for countries outside the US) will be specified in appendix 3 as needed, when IRB and other regulatory submissions are prepared within a specific country.

V3 (November 10th, 2020)

- Added exclusion criteria of intubated patients.
- Added possibility of participation for patients on pravastatin or rosuvastatin.
- Added that patients discharged within 24 hours of enrollment will be ranked as outpatients.
- Update of National Leaders (addition of new countries)
- Replaced Dr. Heresi with Dr. Campos in DSMB (due to the fact that Dr. Heresi declared a COI).

V4 (January 10th, 2021)

- Eliminated possibility of single blinding administration, since with new grant support, full blinding (patient, investigator and adjudicator for symptom questionnaire) can be successfully implemented and mandated at all sites. Of note, no patient has been enrolled in single-label administration. Therefore, the entire trial will be double-blinded.
- Added fenofibric acid as a dose-equivalent preparation (which will be used in Colombia).
- Changed the number of participants enrolled to 700 and added power calculations for primary and secondary outcomes.
- Specified the exclusion of uncontrolled hypothyroidism, allowing enrollment of patients receiving a stable dose of thyroid replacement therapy for at least 6 weeks, with a documented normal TSH (primary hyperthyroidism) or free thyroxine (secondary or tertiary hypothyroidism) level at least 6 weeks after the last dose change. This is because concerns of thyroid myopathy (due to genetic/metabolic effects of thyroid deficiency on skeletal muscle) do not apply to patients who are on adequate thyroid replacement therapy.

V5 (November 2021)

- Included the possibility of enrolling patients from outside of PennMedicine who reach out to us as a result of advertisements. In these instances, it may be necessary to perform laboratory testing through the Center for Human Phenomics Sciences.