1. PROTOCOL AND AMENDMENTS

ORIGINAL PROTOCOL:	01 May 2020
PROTOCOL AMEDMENT 1.0:	12 May 2020

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of the Efficacy and Safety of Intravenous Pamrevlumab, a Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF), in Hospitalized Patients with Acute COVID-19 Disease
PROTOCOL NUMBER:	FGCL-3019-098
PHASE:	Phase 2
STUDY SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
KEY SPONSOR CONTACTS:	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail Address: [redacted] Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail Address: [redacted]
IND NUMBER:	149628
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Hospitalized patients with acute COVID-19 disease due to confirmed SARS-CoV-2 infection
ORIGINAL PROTOCOL:	01 May 2020

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of the Efficacy and Safety of Intravenous Pamrevlumab, a Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF), in Hospitalized Patients with Acute COVID-19 Disease

FGCL-3019-098

Original: 01 May 2020

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents and any applicable local health authority, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

Investigator Name (Printed)		Institution
Signature		Date

Please return a copy of this signature page to FibroGen (or designee). Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 01 May 2020

This protocol is approved by FibroGen.

[redacted] FibroGen, Inc.	DocuSigned by: [redacted]	Date May-20 I 1 :59:15 PDT

1. PROTOCOL SYNOPSIS

PROTOCOL SYNOPSIS	
Study Title:	Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of the Efficacy and Safety of Intravenous Pamrevlumab, a Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF), in Hospitalized Patients with Acute COVID-19 Disease
Protocol Number:	FGCL-3019-098
Investigational Product:	Pamrevlumab (FG-3019)
Study Phase:	Phase 2
Indication:	Hospitalized patients with acute COVID-19 disease due to confirmed SARS-COV-2 infection
Number of Subjects Planned:	Approximately 130
Number of Sites Planned:	Approximately 5-10 in the USA
OBJECTIVES	
To assess the efficacy and safety of pamrevlumab, an investigational monoclonal antibody against connective tissue growth factor (CTGF), compared to placebo, in hospitalized patients with acute COVID-19 disease due to confirmed SARS-COV-2 infection.	

Endpoints
Efficacy Assessments: **Primary Efficacy Endpoint** Proportion of subjects alive and never received mechanical ventilation at Day 14 **Secondary Efficacy Endpoints** • Proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28 • Time to recovery by Day 28 based on 8-point ordinal scale (Day of recovery is defined as the first day on which the patient satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen; 2) Not hospitalized (discharged), but with limitation on activities and/or requiring home supplemental oxygen; 3) Not hospitalized (discharged), with no limitations on activities and not requiring supplemental oxygen • Clinical status based on 8-point ordinal scale (time range: Days 1 to 28) • Days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28 • Days on mechanical ventilation and/or ECMO at Day 28 • Time to mechanical ventilation/ECMO or all-cause mortality at Day 28 • All-cause mortality at Day 28 (proportion of subjects deceased) • Time to death from any cause at Day 28 • Change in PaO_2/FiO_2 ratio as categorical variable using Berlin criteria for ARDS categorization (mild, moderate, severe) (time range: Days 1 to 28) • Change in PaO_2/FiO_2 ratio as continuous variable (time range: Days 1 to 28) • Change in resting SpO_2 adjusted by FiO_2 (time range: Days 1 to 28) • Change in (non-invasive) oxygen supplementation requirements (time range: Days 1 to 28) **Safety Assessments:** Treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs), including hypersensitivity/ anaphylactic reactions; clinical laboratory parameters and vital signs.
STUDY DESIGN
This is a randomized, double-blind, placebo-controlled phase 2 study to evaluate the efficacy and safety of intravenous pamrevlumab, a monoclonal antibody against connective-tissue growth factor (CTGF), in hospitalized subjects with acute COVID-19 disease. Eligible subjects are those with documented SARS-CoV-2 infection, age 40 to 85 years, with evidence of respiratory compromise requiring hospital admission. This age range was chosen to

enhance detection of potential clinical benefits in subjects at highest risk for developing severe COVID-19 disease in this proof-of-concept study.
Approximately 130 subjects will be randomized in a 1:1 ratio to either pamrevlumab or placebo; all subjects will also receive standard-of-care in the judgment of the Investigator.
Study drug administration is via IV infusion on Days 1 (day of randomization), 7, 14 and 28. A follow-up by visit will be performed 4 weeks after the last dose.
All concomitant medications, including approved and non-approved treatments for COVID-19 (e.g., hydroxychloroquine, IL-6 inhibitors, etc.), as well as supplemental oxygenation needs, will be collected and recorded. In addition, the following will be collected and recorded: documentation of SARS-Cov-2 infection, documentation of any other infection(s) prior to or during hospitalization, and whether or not aggressive care is withheld or withdrawn, including the reason for withholding or withdrawal of care (e.g., DNR/DNI order, resource limitation).

STUDY PERIODS

Screening Period: Up to 2 days prior to randomization

Treatment Period: 28 days

Follow-Up Period: 28 days after last dose

SUBJECT ELIGIBILITY CRITERIA

Inclusion Criteria:

1. Age 40-85 years
2. Confirmed SARS-CoV-2 infection by a FDA-authorized diagnostic test (e.g., polymerase chain reaction [PCR] or other approved assay from any specimen source; note: a positive serology/antibody test for SARS-CoV-2 does NOT qualify as evidence of acute COVID-19 disease)
3. Respiratory compromise requiring hospitalization for COVID-19 disease as evidenced by at least one (or more) of the following criteria:
   a. Interstitial pneumonia on CXR or HRCT (findings of consolidation or ground glass opacities), OR
   b. Peripheral capillary oxygen saturation (SpO_2) $\leq$ 94% on room air, OR
   c. Requiring non-invasive supplemental oxygen (e.g., nasal cannula, face mask) to maintain SpO_2
4. Not requiring mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) use at time of randomization
5. Agrees to not participate in another clinical trial for the treatment of COVID-19 disease through Day 28
6. Subject (or legally authorized representative) able to understand and sign a written informed consent form

Exclusion Criteria:

1. Female subjects who are pregnant or nursing
2. Participation in a clinical trial with another investigational drug for COVID-19 disease
3. Anticipated discharge from the hospital or transfer to another hospital or long-term care facility which is not a study site within 72 hours of randomization
4. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies

STUDY TREATMENT

Dose and mode of administration

Dose: 35 mg/kg IV

Dosing regimen: Days 1, 7, 14 and 28.

Other important information

Study drug should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies.

STATISTICAL METHODS

Determination of sample size

The sample size of 65 subjects in each treatment arm will provide approximately 80% power, at 10% two-sided significance level, to detect a 20% absolute difference in the proportion of subjects alive and never received mechanical ventilation at Day 14. This assumes that 65% of subjects in the placebo arm are alive and never received mechanical ventilation at Day 14 compared to 85% in the pamrevlumab group.

Randomization

Subjects who meet all eligibility criteria during screening will be randomized in a 1:1 ratio (pamrevlumab vs placebo) centrally across all sites and based on a pre-determined randomization list from a permuted block design.

Statistical analysis methods

The analysis of the proportion of subjects alive and never received mechanical ventilation at Day 14, the proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28, proportion of subjects' clinical status based on an 8-point ordinal scale, and proportion of subjects with categorical PaO_2/FiO_2 ratio endpoints will be conducted using logistic regression model with treatment group and adjusting for relevant baseline prognostic covariates.

The number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, number of days on mechanical ventilation and/or ECMO at Day 28 will be analyzed using the analysis of covariance (ANCOVA).

Change in PaO_2/FiO_2 ratio to day 28, change in resting SpO_2 adjusted by FiO_2 to day 28, change in (non-invasive) oxygen supplementation requirements to day 28 will be analyzed using Mixed

Model for Repeated Measures (MMRM) approach using relevant prognostic factors as covariates and treatment and Time and treatment *time interaction.
The analysis will take into account the inter-current events as follows.

1. Treatment discontinuation (e.g., due to AEs, Withdrawal by Subject or Physician Decision): Missing endpoint will be imputed by the last result prior to discontinuation.
2. Death: Composite strategy: inter-current event is taken to be a component of the variable. For number of days not requiring mechanical ventilation at Day 14, number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, and number of days on mechanical ventilation and/or ECMO at Day 28; days with missing data after death will be imputed with the worst result until Day 28.
3. Treatment discontinuation due to recovering and discharged from hospital: Missing endpoint will be imputed with the last result prior to discontinuation.

Treatment comparison analysis of time to event endpoints, will be performed using cox regression model adjusting for relevant baseline prognostic factors. Hazard ratios together with 95% two-sided confidence intervals for the hazard ratio will be provided.

Time to recovery by Day 28, time to mechanical ventilation/ECMO or all-cause mortality by Day 28, and all-cause mortality at Day 28 (proportion of subjects deceased), and time to death from any cause at Day 28 will be analyzed using Cox regression adjusting for relevant prognostics factors. Other methods will be used as appropriate.

Safety analyses

All subjects who received any dose of pamrevlumab will be included in the safety population analyses which will summarize treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs), including hypersensitivity/ anaphylactic reactions; clinical laboratory parameters and vital signs.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents.

TABLE OF CONTENTS

2. INTRODUCTION

2.1. Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody that binds to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role (e.g, idiopathic pulmonary fibrosis, certain fibrotic cancers, and Duchenne muscular dystrophy [DMD]). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2. Background Information and Study Rationale

2.2.1. Connective Tissue Growth Factor (CTGF)

CTGF is a 38 kDa secreted matricellular glycoprotein of the cysteine-rich 61/CTGF/nephroblastoma overexpression family (Perbal, 2004, Rachfal, 2005) which was recently renamed cellular communication network (CCN) family (Perbal 2018). It is produced by many cells, including fibroblasts, myofibroblasts, endothelial cells, mesangial cells, and stellate cells.

CTGF is a central mediator of tissue remodeling and fibrosis (Lipson, 2012). CTGF is essential for the fibrotic activity of TGF-B (Mori, 1999, Wang, 2011) but it may also act independently of TGF-B. While much has been made of the role of TGF-B in fibrosis, studies of the role of fibronectin in pulmonary fibrosis showed that the activity of TGF-B is dependent on cellular fibronectin to induce myofibroblast differentiation and that cellular fibronectin may have a fundamental role in activation of latent TGF-B (Muro, 2008). Shi-wen and colleagues showed that critical activities of TGF-B in the fibrotic process are dependent on CTGF expression, including EMT and ECM deposition, supporting the idea that CTGF over-expression is critical for activities attributed to TGF-B (Shi-wen, 2006).

CTGF has been shown to be an important mediator of pulmonary fibrosis in a mouse model of bleomycin-induced pulmonary fibrosis (Bonniaud, 2004). Lasky and coworkers observed upregulation of CTGF messenger ribonucleic acid (mRNA) gene expression in a mouse model of bleomycin-induced pulmonary fibrosis, suggesting a possible role of CTGF in the pathogenesis of lung fibrosis (Lasky, 1998).

2.2.2. Study Rationale

Recent data indicate the presence of interstitial pneumonia (consolidation or ground glass opacities) in a subset of patients infected with novel coronavirus SARS-CoV-2 requiring hospitalization. The interstitial pneumonia is usually bilateral and responsible for reduced efficiency of gas exchange, potentially leading to respiratory failure, intubation and finally death in a significant proportion of patients requiring mechanical ventilation. CTGF (connective tissue growth factor; CCN2) may promote vascular leakage, and administration of pamrevlumab, an investigational anti-CTGF monoclonal antibody, can reverse edema. Using the Miles assay, CTGF promoted vascular leakage in skin (Data on file, generated by FibroGen). In rodent models of complications of diabetes, the abundance of CTGF in urine correlated to the extent of

albuminuria (Roestenberg et al. 2006; FibroGen Report 200_04_3050_034). Pamrevlumab was shown to inhibit vascular leakage in the lungs after irradiation (Bickelhaupt et al. 2017), and in several organs in complications of diabetes models (data on file at FibroGen), as well as to suppress ascites in a genetically engineered model of pancreatic cancer (Neesse et al. 2013). These observations suggest that administration of pamrevlumab may attenuate edema associated with the virus-induced pneumonia and improve gas exchange.

In addition, published data in several animal models (Pi et al. 2018; Bickelhaupt et al. 2017; Sternlicht et al. 2018; Makino et al. 2017; Booth et al. 2010) indicate that pamrevlumab alters trafficking of certain immune-related cells. In a mouse radiation-induced lung fibrosis (RILF) model, the mechanism by which pamrevlumab-treated mice experienced a rapid reversal of pneumonitis appears to be deactivation of myofibroblasts resulting in decreased secretion of inflammatory chemokines (Sternlicht et al. 2018). This hypothesis remains to be confirmed for the RILF model, and the mechanism(s) by which pamrevlumab alters immune cell trafficking remains to be determined. It should also be noted that none of these models involved active viral infections, so it is unclear if pamrevlumab would broadly affect inflammation associated with SARS-Cov-2 infection resulting in COVID-19 disease. However, if blocking CTGF attenuates inflammation, pamrevlumab might reduce symptoms associated with the virus-induced cytokine storm.

In addition to lung damage caused by the immune system's hyperactive attempt to eradicate the viral infection, invasive mechanical ventilation of ARDS patients may also contribute to development of pulmonary fibrosis (Cabrera-Benitez et al. 2014). In ARDS patients that developed fibrosis, there was a statistically significant correlation between ventilator settings and the abundance of TGFB and CTGF in serum (Xie et al. 2019). CTGF has been shown to be elevated in ventilated pre-term sheep, and to increase with gas volume (Wallace et al. 2009) and flow (Bach et al. 2008). CTGF expression also increases with tidal volume in neonatal rats (Wu et al. 2008). In ventilator-induced lung injury (VILI) models with adult rats, macrophages were reported to mediate disruption of epithelial barrier function and edema (Frank et al. 2006; Eyal et al. 2007). Interestingly, in the RILF model, macrophages represented the most enriched cell type induced by radiation damage, which were subsequently normalized by therapeutic pamrevlumab administration (Bickelhaupt et al. 2017; Sternlicht et al. 2018). Together, these data suggest that CTGF may mediate some aspects of ventilator-induced lung damage and that pamrevlumab may attenuate some of the damage.

Hyperoxia may also contribute to acute lung injury in intubated ARDS patients (Schwarz 2001). In the rat neonatal hyperoxia model of bronchopulmonary dysplasia, an antibody with activity similar to that of pamrevlumab was able to improve lung development in non-ventilated pups (Alapati et al. 2011). This suggests that pamrevlumab might attenuate some of the pathology associated with hyperoxia.

Pathophysiology resulting from SARS-Cov-2 may lead to interstitial lung fibrosis in patients that survive the infection. Data from a retrospective cohort study in Wuhan, China (Zhou F Lancet 2020) show that more than one-third of COVID-19 patients surviving pneumonia have residual respiratory failure, due to fibrotic changes in the lung. Approximately 15-30% of patients hospitalized for COVID-19 develop acute respiratory distress syndrome (ARDS) (Wang et al. 2020; Chen et al. 2020; Huang et al. 2020). Patients that survive ARDS often develop fibrosis

within 3-4 weeks (Zapol et al. 1979), and the onset of fibrotic changes can begin as early as 36 hours after lung injury (Schwarz 2001). The distribution and composition of extracellular matrix (ECM) within the alveolar wall is similar in both ARDS and idiopathic pulmonary fibrosis (IPF) (Raghu et al. 1985), suggesting that pamrevlumab, which has demonstrated antifibrotic effects in IPF patients (Raghu et al. 2016; Richeldi et al. 2020), might help in reducing residual fibrotic damage in lungs of patients with COVID-19.

CTGF is a key mediator of pro-fibrotic pathways that has a very complicated biology (Lipson et al. 2012). Considered together, the data above suggest that its inhibition might mitigate interstitial fibrosis in the post-acute infection setting via multiple mechanisms. In addition, it might attenuate edema acutely associated with ARDS and VILI, which may improve gas exchange.

This clinical study has been prepared based on these rationales to address the current medical emergency, given the extremely high number of patients affected by COVID-19 disease.

2.3. Summary of Past Clinical Studies, Safety and Dosing Information

The clinical trial experience with pamrevlumab includes 11 completed clinical studies to date. A total of 624 subjects have received investigational drug and/or standard of care in these clinical trials, including 270 subjects with IPF, 112 subjects with pancreatic cancer, 21 pediatric subjects with DMD, 112 subjects with liver fibrosis secondary to hepatitis B, 107 subjects with DN, and 2 pediatric subjects with focal segmental glomerulosclerosis (FSGS). Approximately 530 subjects have received pamrevlumab across these clinical trials. There are studies currently ongoing in patients with IPF, pancreatic cancer, and DMD.

Adverse events (AEs) have been generally mild or moderate in severity and transient in duration. The AEs have been typical of the patients' underlying medical condition(s) and, in placebo-controlled studies, were equally distributed between the placebo and pamrevlumab treatment groups. Infusions of pamrevlumab have been well tolerated. There is no apparent pattern to the serious adverse events (SAEs) observed during clinical trials.

In a placebo-controlled Phase 2 IPF study of approximately 100 patients, pamrevlumab was well tolerated, with a safety profile similar to that of placebo. The placebo group reported more TEAEs of cough (43%) than in the pamrevlumab group (28%). TESAEs were observed in 12 patients (24%) in the pamrevlumab group and 8 (15%) in the placebo-group and were mostly respiratory-related; however, fewer patients in the pamrevlumab group discontinued study treatment because of a TESAE than did those in the placebo group., and fewer patients in the pamrevlumab group (5 [10%]) compared to placebo (7 [13%]) were hospitalized following a respiratory-related TESAE. Nine patients died during the study: three (6%) in the pamrevlumab group and sic (11%) in the placebo group.

A Phase 2 dose-response study of pamrevlumab was performed in pancreatic cancer patients (Picozzi et al. (2017) J Clin Cancer Trials 2:1). In this study, pamrevlumab (FG-3019) was administered every two weeks at doses up to 45 mg/kg, or weekly at 22.5 mg/kg after a loading dose of 45 mg/kg. Patients that had trough plasma levels of pamrevlumab immediately before the second dose that was greater than 150 µg/ml exhibited better overall survival than those whose plasma trough levels were less than 150 µg/ml. Patients that had ascites exhibited lower plasma levels of pamrevlumab than patients without ascites. This may be because ascites fluid

contains significant amounts of CTGF (data on file), and therefore may act as a sink for administered antibody. Patients with ascites that achieved high trough levels of pamrevlumab (>150 µg/ml) had a median overall survival that was about 4 times longer than those that had lower trough levels (8.7 vs. 1.9 months). Together, these data suggest that it is important to achieve high plasma exposure to pamrevlumab in order to achieve maximal benefit.

In a Phase 2 open label, study, randomized study in locally advanced unresctable pancreatic cancer LAPC), patients received 35mg/kg on days 1, 7 and 14 and then after every two weeks for total of six month in combination with gemcitabine and paclitaxel vs. combination of gemcitabine and paclitaxel. No safety concerns were seen with this dosing regimen and a phase 3 study in LAPC is ongoing.

In an open label study in patients age 12 and above with non-ambulatory Duchenne Muscular Dystrophy (DMD), pamrevlumab has been administered at 35mg/kg, every 2 weeks, for nearly two years with no safety concerns identified. Considered together, the data suggest that three weekly doses of pamrevlumab at 35 mg/kg, followed by bi-weekly administration for several more months should be well tolerated.

Supporting the dosing regimen of 35 mg/kg, dosed weekly until Day 14, followed by every 2 weeks for the remaining treatment period, are data from the PRAISE clinical trial. PRAISE was a phase 2 placebo-controlled study in IPF with administration of pamrevlumab once every three weeks at 30 mg/kg, for 48 weeks. In PRAISE, the rate of FVC loss in the pamrevlumab-treated group was indistinguishable from that of placebo for the first 12 weeks, after which the rate of loss in the pamrevlumab-treated subjects was significantly slower (Richeldi et al, 2019). This observation suggests that adequate exposure to pamrevlumab to manifest its activity in IPF patients was not achieved until about the 4^{th} or 5^{th} dose when it was administered at 30 mg/kg every 3 weeks. Repeat dose pharmacokinetic (PK) data in non-human primates indicates that achievement of steady-state levels of circulating pamrevlumab requires multiples doses, and that this is achieved faster at higher and more frequent doses. Computer modeling of pamrevlumab PK in humans also suggests that addition of at least one “loading dose” will result in more rapid achievement of efficacious plasma levels. This is the reason for the proposed dosing regimen in this acute-care setting.

Over the course of the entire study, there were numerically more subjects with a HAHA response in the pamrevlumab group than in the placebo group. During the main study randomized treatment period, 2 subjects in the placebo group had a sample that was both specific and reactive for antibodies to pamrevlumab. In the open-label extended treatment period, 7 subjects had samples that were specific and reactive: 2 subjects who were randomized to receive pamrevlumab and 5 subjects that were randomized to receiving placebo. In a sub-study, 2 subjects had specific and reactive samples, 1 subject in the pamrevlumab/pirfenidone group and 1 subject in the pamrevlumab/nintedanib group.

Overall, incidence of apparent HAHA within the group was low and the signal was detected at a low titer. Therefore FibroGen believes that these HAHA responses are most likely due to non-specific assay variability. However, FibroGen will continue to assess the impact of immunogenicity and neutralizing antibody (if any) in future studies.

In summary, pamrevlumab has been shown to be well tolerated. For additional information on the safety of pamrevlumab in IPF patients and in other indications, please refer to the current version of the Investigator's Brochure.

2.3.1. Clinical efficacy in completed studies:

Two studies of pamrevlumab in subjects with pancreatic cancer have demonstrated preliminary evidence of efficacy as measured by OS and by eligibility for surgical exploration and resection.

The results of an open-label Phase 2 study and a randomized, placebo-controlled Phase 2 study suggests pamrevlumab slows the progression of IPF as measured by change in FVC % predicted, quantitative analysis of fibrosis, and time to disease progression or death. (King 2009; Raghu et al, 2004; Zisman et al, 2010; King et al, 2014; Richeldi et al, 2014; Raghu et al. 2016, Clukers et al. 2018; Richeldi et al, 2019).

2.4. Ongoing clinical study in patients with SARS-CoV-2 Infection

An Investigator-Initiated Phase 2/3 open-label, randomized, parallel-arm study investigating the efficacy and safety of intravenous administration of pamrevlumab versus standard of care in patients with COVID-19 disease due to SARS-CoV-2 infection has recently been initiated in Italy: Study FGCL-3019-IST-014.

3. OBJECTIVES AND ASSESSMENTS

3.1. Objective

To assess the efficacy and safety of intravenous pamrevlumab, an investigational monoclonal antibody against connective-tissue growth factor (CTGF), compared to placebo, in hospitalized patients with acute COVID-19 disease due to confirmed SARS-COV-2 infection.

3.2. Efficacy Assessments

Primary Efficacy Endpoint

Proportion of subjects alive and never received mechanical ventilation at Day 14

Secondary Efficacy Endpoints

- Proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28
- Time to recovery by Day 28 based on 8-point ordinal scale (Day of recovery is defined as the first day on which the patient satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen; 2) Not hospitalized (discharged), but with limitation on activities and/or requiring home supplemental oxygen; 3) Not hospitalized (discharged), with no limitations on activities and not requiring supplemental oxygen
- Clinical status based on 8-point ordinal scale (time range: Days 1 to 28)
- Days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28
- Days on mechanical ventilation and/or ECMO at Day 28
- Time to mechanical ventilation/ECMO or all-cause mortality at Day 28
- All-cause mortality at Day 28 (proportion of subjects deceased)
- Time to death from any cause at Day 28
- Change in PaO_2/FiO_2 ratio as categorical variable using Berlin criteria for ARDS categorization (mild, moderate, severe) (time range: Days 1 to 28)
- Change in PaO_2/FiO_2 ratio as continuous variable (time range: Days 1 to 28)
- Change in resting SpO_2 adjusted by FiO_2 (time range: Days 1 to 28)
- Change in (non-invasive) oxygen supplementation requirements (time range: Days 1 to 28)

3.3. Safety Assessments

Treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs), including hypersensitivity/ anaphylactic reactions; clinical laboratory parameters and vital signs.

4. OVERALL STUDY DESIGN

This is a randomized, double-blind, placebo-controlled phase 2 study of the efficacy and safety of intravenous pamrevlumab, a monoclonal antibody against connective-tissue growth factor (CTGF), in hospitalized subjects with acute COVID-19 disease due to SARS-CoV-2 infection.

Eligible subjects are those with documented SARS-CoV-2 infection, age 40 to 85 years, with evidence of respiratory compromise requiring hospital admission. This age range was chosen to enhance detection of potential clinical benefits in subjects at highest risk for developing severe COVID-19 disease in this proof-of-concept study.

The total sample size is approximately 130 subjects. Subjects are randomized in a 1:1 ratio, according to a pre-determined randomization list from a permuted block design.

Study drug will be administered as IV infusion on Days 1 (day of randomization), 7, 14 and 28. A follow-up by visit will be performed 4 weeks after the last dose.

All subjects will be treated with standard-of-care according to the judgment of the Investigator. All concomitant treatments, including approved and non-approved therapies for COVID-19 disease, will be collected and recorded (see also Section 6.3).

Safety will be intensively monitored throughout the study. A detailed overview of collection of assessments is provided in Section 6 and Schedule of Assessments (SOA).

4.1. Subject ID Assignment

Subjects that sign consent will be assigned an 8 digit Subject ID number consisting of a four digit site number and a 4 digits Subject ID starting with 1xxx. Subject numbering will be assigned sequentially as subjects are recruited/screened (e.g., 1001, 1002, and 1003, etc.).

4.2. Randomization

Subjects who meet the eligibility criteria during screening will be randomized in a 1:1 ratio (pamrevlumab vs placebo) centrally across all sites.

Automated randomization and treatment assignments will be performed by an Interactive Response System (IXRS or IRT).

4.3. Blinding

This is a double-blind, placebo-controlled study. The Investigator, study site staff, subjects, selected sponsor clinical team and designees are blinded to study drug assignment. Blinded treatment with a placebo control is the gold standard method for obtaining unbiased assessments of safety and efficacy in clinical trials of investigational drugs such as pamrevlumab.

The study blind will be maintained for all parties specified above throughout the study. Pamrevlumab and placebo will be identical in appearance, packaging, and labeling in order to maintain the study blind.

4.3.1. Request for Unblinding of Treatment Assignment

Investigators, study site staff and subjects will remain blinded to treatment assignments until study completion and database lock.

Breaking the blind during the study (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator due to immediate safety concerns, or is considered essential for the immediate subject management, and should be discussed with the Medical Monitor beforehand, if possible. It is the responsibility of the investigator to promptly document and explain any unblinding to the sponsor.

4.4. Study Duration

The Screening Period is up to 2 days prior to randomization, to confirm eligibility.

The Treatment Period is 28 days. Study drug will be administered as IV infusion on Days 1 (day of randomization), 7, 14 and 28.

The Follow-Up Period is 28 days after the last dose.

Visits /assessments will occur every day for 28 days, or until hospital discharge, whichever occurs earlier. If a subject is discharged prior to Day 14 or Day 28, the subject should return as outpatient on Days 14 and/or Day 28, for study drug infusions and assessments.

Subjects who withdraw from the study early, for any reason, will need to return for an Early Study Withdrawal /Termination visit 28 days (+7 Days) after the last infusion and may be contacted by phone at Day 14 and 28 to check the subject's survival status.

See also Section 6 for additional detail.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

In order to be eligible for inclusion in this trial, a Subject must meet all of the following:

1. Age 40-85 years
2. Confirmed SARS-CoV-2 infection by a FDA-authorized diagnostic test (e.g., polymerase chain reaction [PCR] or other approved assay from any specimen source; note: a positive serology/antibody test for SARS-CoV-2 does NOT qualify as evidence of acute COVID-19 disease)
3. Respiratory compromise requiring hospitalization for COVID-19 disease as evidenced by at least one (or more) of the following criteria:
    a. Interstitial pneumonia on CXR or HRCT (findings of consolidation or ground glass opacities), OR
    b. Peripheral capillary oxygen saturation (SpO_2) $\leq$ 94% on room air, OR
    c. Requiring non-invasive supplemental oxygen (e.g., nasal cannula, face mask) to maintain SpO_2
4. Not requiring mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) use at time of randomization
5. Agrees to not participate in another clinical trial for the treatment of COVID-19 disease through Day 28
6. Subject (or legally authorized representative) able to understand and sign a written informed consent form

5.2. Exclusion Criteria

Subjects will be excluded from this trial if any of the following apply:

1. Female subjects who are pregnant or nursing
2. Participation in a clinical trial with another investigational drug for COVID-19 disease
3. Anticipated discharge from the hospital or transfer to another hospital or long-term care facility which is not a study site within 72 hours of randomization
4. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies

5.3. Study Withdrawal Criteria

Subjects may withdraw from the study at any time, for any reason. Reasons for discontinuing will be documented and Subjects are encouraged to have a final follow-up visit (in person or by phone) to check on the general health of the subject.

Reasons for withdrawing the Subject from the study include the following:

- Any safety concern in the Investigator's opinion, that precludes further study participation
- Female subjects who are pregnant or nursing
- Participation in a clinical trial with another investigational drug for COVID-19 disease
- Withdrawal of Consent

5.4. Replacement of Study Subjects

All randomized subjects will be included in the study. Subjects who terminate the study early will not be replaced.

5.5. Study Closure

FibroGen reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of the study site or termination of the study by FibroGen may include (but are not limited to):

- Successful completion of the study at the investigational site
- The required number of subjects for the study has been recruited
- Failure of the Investigator to comply with the protocol, GCP guidelines or local requirements
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

6. STUDY ASSESSMENTS

6.1. Laboratory Assessments, including ABG and SpO2

Labs will be collected locally for safety and include hematology: CBC (complete blood count) and differential, chemistry: CMP (Comprehensive Metabolic Panel), and routine coagulation panel (INR, PT, aPTT).

Arterial blood gas (ABG) will be collected each day the patient is in ICU/CCU, and recorded anytime if performed as part of routine care outside ICU/CCU, while hospitalized.

Peripheral capillary oxygen saturation (SpO2) will be collected each day while hospitalized.

6.2. Modified WHO Ordinal Scale

Assessment of clinical status, using an 8-Point, Modified WHO Ordinal Scale as specified below, should be assessed daily, until Day 28:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitations on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen, no longer requiring medical care
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19-re;ated or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, requiring nasal high-flow oxygen, non-invasive mechanical ventilation, or both
7. Hospitalized, requiring invasive mechanical ventilation, extra-corporeal membrane oxygenation (ECMO), or both
8. Death

6.3. Concomitant Medications, Supplemental Oxygen Needs, and other Care

Subjects will be treated according to best available standard-of-care according to the judgment of the Investigator. All concomitant medications, including approved and non-approved treatments for COVID-19 (e.g., hydroxychloroquine, IL-6 inhibitors, etc.), as well as supplemental oxygen needs, will be collected and recorded.

In addition, the following will be recorded and collected: documentation of SARS-Cov-2 infection, documentation of any other infection(s) prior to or during hospitalization, and whether or not aggressive care is withheld or withdrawn, including the reason for withholding or withdrawal of care (e.g., DNR/DNI order, resource limitation).

7. STUDY DRUG

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF and is formulated as solution for administration by IV infusion.

Pamrevlumab is supplied in single-use glass vials containing sterile, preservative-free solution (100 mg pamrevlumab/vial or 500 mg pamrevlumab/vial respectively). The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL L-histidine, 3.08 mg/mL L-histidine HCl, 8.01 mg/mL sodium chloride, and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

Matching placebo is formulated as solution to be administered in a manner that is identical to pamrevlumab infusion.

7.1. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice requirements for labelling and local regulatory guidelines.

7.2. Study Drug Storage

Study drug vials must be stored refrigerated (2°C to 8°C), in a temperature- controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation. Details regarding the reporting of temperature excursions can be found in the study Investigational Product (IP) Manual.

7.3. Study Drug Preparation

Study drug is infused undiluted after pooling the contents of the calculated number of vials in an empty infusion bag (total volume of fluid must not exceed **410 mL**) according to the Dose Preparation Instructions in the IP Manual.

Study drug solutions for infusion must be stored refrigerated (2°C to 8°C) and administered within 24 hours of preparation and administered within 6 hours of stored at room temperature. Study drug infusion solutions are administered by IV infusion, using an infusion set with a 0.2 µm in-line filter.

7.4. Study Drug Administration

Dosing will be based on the weight obtained on Day 1. The total dose **is not to exceed 4.1g**. The dose should be prepared in a **volume of fluid that does not exceed 410 mL**. Study drug will be administered as soon as possible after release from the site's pharmacy and infused within 24 hours of preparation. Study drug will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

The first infusion shall be completed in approximately 2 hours. If the first infusion is well tolerated and no infusion related AEs are observed during the infusion or subsequent 1-hour observation period, the second infusion shall be completed in approximately 1 hour. The 2

subsequent infusion periods may be shortened to approximately 30 minutes if no infusion-related AEs were observed.

If an infusion-related AE occurs during the subsequent infusion, study drug will be administered over approximately 1 hour for the next three infusions. If no drug-related AEs are observed in any of these three infusions, the duration of infusion may be decreased to approximately 30 minutes.

The Investigator or other qualified personnel must be either present, or immediately available, during all infusions and observation periods for each Subject. If a Subject has a significant infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms.

Medications for the treatment of acute reactions, including anaphylaxis, must be available to study site staff for immediate use. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

7.5. Study Drug Handling and Disposal

All study drug must be controlled and tracked. Drug accountability and reconciliation for all study drug received should be completed by the study site. All used, unused, and partially used study drug should be destroyed on site according to local/institutional policies by the pharmacy/authorized staff with approval from Sponsor (or designee), and destruction records maintained. IV bags used to infuse study drug can be disposed of per institutional policy.

8. ASSESSMENTS OF SAFETY

8.1. Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the study drug.

8.2. Definitions

8.2.1. Definition of an Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject as defined in the study protocol are recorded in the subject's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery, or a medical procedure while on study, is not considered an adverse event.

8.2.2. Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or

- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the primary cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be a SAE.

Scheduled or pre-planned hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures (including elective procedures) do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1. Adverse Event Reporting Period

The safety reporting period begins after the subject has signed the informed consent and ends 28 days after the last dose of study drug. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5). Pregnancy reporting requirements are outlined in Section 8.3.6.

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will actively seek information from each subject at each visit to collect any AEs occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit. There will be no directed questioning for any specific AE. This does not deter the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse

event. The investigator is expected to follow reported adverse events until stabilization or reversibility.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the most current National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE v5.0) guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death**: Fatal AE.

8.3.4. Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order

to appropriately describe the safety profile of the study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- Related:
  - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- Not Related:
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5. Reporting Serious Adverse Events (SAEs)

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through 28 days after the last dose of pamrevlumab are recorded in the subject's medical record and are submitted to FibroGen. All SAEs must be submitted to FibroGen within 24 hours following the investigator's knowledge of the event via the SAE report form. Additionally, pamrevlumab related SAEs (including deaths) that occur after the EOS/safety follow-up visit will be reported.

If a subject is permanently withdrawn from protocol required therapies because of a serious adverse event, this information must be submitted to FibroGen. FibroGen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and central IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

8.3.5.1. Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations and IRB/EC requirements. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2. Deaths

The investigator will report the fatal event to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.4.

If the death occurred within the AE collection and reporting period (signed ICF to 28 days after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. If the investigator becomes aware of a death occurring after the AE reporting period and considers it related to pamrevlumab, it will be reported as an SAE.

8.3.6. Pregnancies: Reporting and Follow-up of Subjects and Female Partners of Subjects

The outcome of all pregnancies for female subjects or female partners of male subjects should be followed up and documented as described. If a female subject or a female partner of a male subject becomes pregnant while the subject is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to the Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a

Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

Pregnancy itself is not an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the subject was discontinued from the study. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If a lactation case occurs while the female subject is taking protocol-required therapies, or within 28 days after the last dose of study treatment, report the lactation case to FibroGen. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the last dose of pamrevlumab. Any lactation case should be reported to FibroGen's Safety within 24 hours of the investigator's knowledge of event.

8.3.7. Laboratory or other Test Abnormalities/ Findings

A laboratory or other test abnormality (e.g., spirometry, HRCT) in the absence of any signs or symptoms is not necessarily an AE. The investigator must review and assess all test results provided by the central laboratory or other vendors throughout the study in a timely manner, and determine whether any abnormal values/test results are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Such abnormalities should be considered CS if they are associated with new signs or symptoms, if they occur after taking study medication, reflect a meaningful change from the screening value(s), or require active management (e.g., requiring treatment, additional testing, study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

Clinically significant laboratory abnormalities will be reported as AEs. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8. Hypersensitivity/Anaphylactic Reactions:

Hypersensitivity and anaphylactic reactions will be monitored throughout the study, using the criteria below as defined per Sampson et al. 2006 (Sampson, 2006).

Anaphylaxis is highly likely when the following criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

And at least one of the following criteria:

a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

8.3.9. Safety Monitoring

Safety will be assessed throughout the study. A medically complete baseline profile of each subject will be established through medical history, a complete physical examination including vital signs, laboratory tests and PFTs. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Safety and tolerability will be monitored closely by FibroGen.

8.3.9.1. Special Reporting Situations

Special Reporting Situations on FibroGen investigational product Pamrevlumab that require safety evaluation include:

- Overdose (any dose greater than 4.1g)
- Suspected abuse/misuse
- Inadvertent or accidental exposure
- Medication error (e.g. incorrect dose administered)
- Drug-drug interactions

Report special situations to FibroGen’s Safety within 24 hours of the investigator’s knowledge of the event. See Study Reference Manual for detailed reporting instructions.

9. STATISTICS

9.1. Sample Size Determination

The sample size of 65 subjects in each treatment arm will provide about 80% power, at 10% two-sided significance level, to detect a 20% difference in the proportion of subjects alive and never received mechanical ventilation at Day 14. This assumes that 65% of subjects in the placebo arm are alive and never received mechanical ventilation at Day 14 compared to 85% in the pamrevlumab group.

9.2. Analysis Populations

Enrollment and disposition summaries will be provided on all randomized subjects.

The Safety Population consists of all subjects who have received at least one dose of study drug. All safety summaries will be based on the Safety Population.

The Intent-To-Treat Set (ITT) consists of all randomized subjects. All efficacy analyses will be performed based on the ITT set.

9.3. General Considerations

Baseline value is defined as mean of all screening and Day 1 values prior to the first dose.

Descriptive summaries will be presented for study parameters including baseline characteristics, safety, and efficacy.

Continuous variables will be reported in mean, standard deviation or standard error, median, Q1-Q3, minimum, and maximum.

Categorical variables will be reported in frequency and percentage of subjects within each outcome category.

9.4. Statistical Methods

The analysis of the proportion of subjects alive and never received mechanical ventilation at Day 14, the proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28, proportion of subjects' clinical status based on an 8-point ordinal scale, and proportion of subjects with categorical PaO_2/FiO_2 ratio endpoints will be conducted using logistic regression model with treatment group and adjusting for relevant baseline prognostic covariates.

The number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, number of days on mechanical ventilation and/or ECMO at Day 28 will be analyzed using the analysis of covariance (ANCOVA).

Change in PaO_2/FiO_2 ratio to day 28, change in resting SpO_2 adjusted by FiO_2 to day 28, change in (non-invasive) oxygen supplementation requirements to day 28 will be analyzed using Mixed Model for Repeated Measures (MMRM) approach using relevant prognostic factors as covariates and treatment and Time and treatment *time interaction

The analysis will take into account the inter-current events as follows:

1. Treatment discontinuation (e.g., due to AEs, Withdrawal by Subject or Physician Decision): Missing endpoint will be imputed by the last result prior to discontinuation.
2. Death: Composite strategy: inter-current event is taken to be a component of the variable. For number of days not requiring mechanical ventilation at Day 14, number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, and number of days on mechanical ventilation and/or ECMO at Day 28; days with missing data after death will be imputed with the worst result until Day 28.
3. Treatment discontinuation due to recovering and discharged from hospital: Missing endpoint will be imputed with the last result prior to discontinuation.

Treatment comparison analysis of time to event endpoints, will be performed using cox regression model adjusting for relevant baseline prognostic factors. Hazard ratios together with 95% two-sided confidence intervals for the hazard ratio will be provided.

Time to recovery by Day 28, time to mechanical ventilation/ECMO or all-cause mortality by Day 28, and all-cause mortality at Day 28 (proportion of subjects deceased), and time to death from any cause at Day 28 will be analyzed using Cox regression adjusting for relevant prognostics factors. Other methods will be used as appropriate.

9.5. Safety Analyses

All subjects who received any dose of pamrevlumab will be included in the safety analyses which will summarize treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs); clinical laboratory parameters and vital signs, as well as hypersensitivity/anaphylactic reactions.

10. ETHICS

10.1. Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirements, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

This protocol, the Informed Consent Form, and the Investigator's Brochure must be approved by a properly constituted IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator.

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

Prior to participation in any study-specific procedures, the subject (or legally authorized representative) must sign an IRB/IEC-approved written Informed Consent Form (ICF) in his/her native language.

10.2. Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining re-approval by the IRB/IEC annually or as required by the policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required reports submitted to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen or designee. A copy of the signed FDA Form 1572 or other qualified investigator statement (as required) must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen or its designee. Written documentation of IRB/IEC approval must be received before the amendment is implemented.

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

10.3. Subject Information and Consent

Prior to participation in any study-specific procedures, the subject must sign (note: all references to "subject" in this section refers to the study subject or his/her legally acceptable representative) an IRB/IEC-approved written Informed Consent Form (ICF) in his/her native language. The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the subjects. To obtain and document informed consent, the Investigator should comply with applicable regulations, and adhere to ICH GCP standards.

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and IRB/IEC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of the signed and dated ICF.

If there are any changes to the IRB/IEC approved ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF, if/as required by the IRB/IEC.

Each subject (or legally authorized representative) must provide his or her consent for the use and disclosure of personal health information in accordance with applicable regulatory requirements.

10.4. Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent or other disclosure authorization documents signed by the subject, unless permitted or required by applicable law.

11. DATA HANDLING AND RECORD KEEPING

11.1. Source Documents

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. The investigator or designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the Case Report Forms (CRFs) and resolved queries.

11.2. Direct Access to Source Documents

The investigator must provide direct access to source data and source documents for trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspection. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information and medical records.

11.3. Data Collection, Handling, and Verification

All required data will either be entered onto CRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data (i.e. CRFs and queries) throughout the duration of the study and prior to study completion, ensuring that all data are verifiable with source documents.

11.4. Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, FibroGen, and to the regulatory authorities, if required.

11.5. Retention of Data

A FibroGen representative will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or FibroGen or designee, the Investigator agrees to keep records, including the identity of all participating subjects (eg, subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of drug disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the Investigator may need to retain these documents for a longer period if required by applicable law, regulatory requirements or by an agreement with FibroGen whichever is longer.

11.6. Financial Disclosure

The Investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The Investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 or other qualified investigator statement must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study. The Investigator Financial Disclosure Form for any Investigator(s) leaving the clinical site prior to study completion will be obtained prior to study completion.

12. PUBLICATION POLICY

The data and results of the study will be owned solely by FibroGen and shall be confidential information of FibroGen, subject to the Investigator's publication rights, described below and if any outlined in the Clinical Trial Agreement. It is understood by the Investigator that FibroGen may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators, the Licensing Authority or to regulatory agencies of other governments. To allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to FibroGen.

Any publication or presentation of the results of this clinical study by the Investigator may only be made in strict compliance with the provisions of the Clinical Trial Agreement. Any publication relating to the study shall be made in collaboration with FibroGen. The Investigator should understand that it is not FibroGen’s intention to prevent publication of the data generated in the clinical study. However, FibroGen reserves the right to control the form and timing of such publication for commercial reasons. The Study Center and Investigator shall adhere to the publication language as outlined in both Clinical Trial Agreement and the protocol to the extent that if there is any conflict or ambiguity between Clinical Trial Agreement and the protocol, the publication terms in the Clinical Trial Agreement shall prevail.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening	**Treatment**							**4-Weeks after Last Dose**
	Up to 2 days prior to Day 1	Day 1	Days 2-6[6]	Day 7	Days 8-13[6]	Day 14	Days 15-27 [6]	Day 28	
Informed consent	X								
Eligibility criteria	X								
Medical History	X								
Demographic information	X								
Vital signs	X	X[1]	X	X[1]	X	X[1]	X	X[1]	
Urine pregnancy test[2]	X								
Concomitant medication and non-drug therapies	X	X	X	X	X	X	X	X	X
Infusion		X		X		X		X	
Local laboratory tests (hematology: CBC and differential, chemistry: CMP, coagulation parameters: INR, PT, aPTT)		X		X		X		X	X
Arterial Blood Gasses (ABG) [5]	X	X	X	X	X	X	X	X	
Resting SpO2 [4]	X	X	X	X	X	X	X	X	
Oxygen Supplementation Needs[3, 4]	X	X	X	X	X	X	X	X	
WHO Ordinal Scale		X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X
Survival, ICU and Hospital Discharge Status		X	X	X	X	X	X	X	X

[1] On infusion days, vitals taken within 30 minutes prior and 30 min after infusion; otherwise vitals taken daily [2] Women of child-bearing potential.
[3] Need for mechanical ventilation/ECMO, including ventilator settings, or supplemental oxygen, including mode of oxygen delivery. [4] Collected until Day 28 or hospital discharge, whichever occurs earlier [5] ABGs are collected daily while in ICU/CCU, and recorded if performed as part of routine care outside of ICU/CCU, until Day 28 or hospital discharge, whichever occurs earlier [6] if subject is discharged, these visit do not apply; subject should return for infusion visits only.

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of the Efficacy and Safety of Intravenous Pamrevlumab, a Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF), in Hospitalized Patients with Acute COVID-19 Disease
PROTOCOL NUMBER:	FGCL-3019-098
PHASE:	Phase 2
STUDY SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
KEY SPONSOR CONTACTS:	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail Address: [redacted] Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail Address: [redacted]
IND NUMBER:	149628
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Hospitalized patients with acute COVID-19 disease due to confirmed SARS-CoV-2 infection
ORIGINAL PROTOCOL:	01 May 2020
AMEDMENT 1.0:	12 May 2020

INVESTIGATOR SIGNATURE PAGE
STUDY ACKNOWLEDGEMENT

Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of the Efficacy and Safety of Intravenous Pamrevlumab, a Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF), in Hospitalized Patients with Acute COVID-19 Disease

FGCL-3019-098

Original: 01 May 2020

Amendment 1.0: 12 May 2020

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents and any applicable local health authority, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

Investigator Name (Printed)		Institution
Signature		Date

Please return a copy of this signature page to FibroGen (or designee). Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 01 May 2020

Amendment 1.0: 12 May 2020

This protocol is approved by FibroGen.

[redacted] FibroGen, Inc.	DocuSigned by: [redacted]	Date 23-May-20 I 16 45:29 PDT

AMENDMENT 1.0: KEY CHANGES FROM ORIGINAL PROTOCOL

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, flow, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Description of Key Change	Rationale for Change	Section(s) Affected
Primary Endpoint updated to include proportion of subjects who never received mechanical ventilation and/or ECMO and are alive at Day 28	Per FDA feedback modified the time point of the primary endpoint to ensure a sufficient number of events will occur	Synopsis, Sections 3.2, 9.1, and 9.4
Secondary Endpoint added to include proportion of subjects who never received mechanical ventilation and/or ECMO and are alive at Day 14	Added additional secondary endpoint to further assess events at Day 14	Synopsis and Sections 3.2 and 9.4
Subjects who do not receive all study drug doses, will be encouraged to continue with all study visits and assessments	Per FDA feedback, updated to collect data on all comers and to prevent missing data	Section 4.4 and 5.3
Added distinction between Treatment Discontinuation and Study Withdrawal, and clarified that subjects who discontinue treatment are encouraged to remain on study. Specified mandatory reasons for study withdrawal	Per FDA feedback, updated to ensure lost to follow-up is a specific reason for withdraw and clarified withdraw treatment criteria.	Section 5.3
Clarify that vital status can be obtained from public records	Per FDA feedback, add to support the collection of data and to prevent missing data	Section 6.3
Clarify that all new or worsened lab abnormalities should be reported as adverse events	Per FDA feedback, updated language to clarify that lab abnormalities will be recorded as AEs	Section 8.3.7
Added Data Monitoring Committee (DMC)	Per FDA feedback, added that a DMC will be utilized	Section 8.3.9.2

Added Interim Safety Analysis as part of the DMC Responsibilities	Per FDA feedback, an interim analysis for safety is added as part of the DMC responsibilities	Section 8.3.9.2
Added that visits can be conducted remotely	Per FDA, to maximize data collection allow for remote visits	Section 5.3, Schedule of Assessments

1. PROTOCOL SYNOPSIS

PROTOCOL SYNOPSIS	
Study Title:	Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of the Efficacy and Safety of Intravenous Pamrevlumab, a Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF), in Hospitalized Patients with Acute COVID-19 Disease
Protocol Number:	FGCL-3019-098
Investigational Product:	Pamrevlumab (FG-3019)
Study Phase:	Phase 2
Indication:	Hospitalized patients with acute COVID-19 disease due to confirmed SARS-COV-2 infection
Number of Subjects Planned:	Approximately 130
Number of Sites Planned:	Approximately 5-10 in the USA
OBJECTIVES	
To assess the efficacy and safety of pamrevlumab, an investigational monoclonal antibody against connective tissue growth factor (CTGF), compared to placebo, in hospitalized patients with acute COVID-19 disease due to confirmed SARS-COV-2 infection.	

Endpoints
Efficacy Assessments: **Primary Efficacy Endpoint** Proportion of subjects who never received mechanical ventilation and/or ECMO and alive at Day 28 **Secondary Efficacy Endpoints** • Proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28 • Proportion of subjects who never received mechanical ventilation and/or ECMO and alive at Day 14 • Time to recovery by Day 28 based on 8-point ordinal scale (Day of recovery is defined as the first day on which the patient satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen; 2) Not hospitalized (discharged), but with limitation on activities and/or requiring home supplemental oxygen; 3) Not hospitalized (discharged), with no limitations on activities and not requiring supplemental oxygen • Clinical status based on 8-point ordinal scale (time range: Days 1 to 28) • Days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28 • Days on mechanical ventilation and/or ECMO at Day 28 • Time to mechanical ventilation/ECMO or all-cause mortality at Day 28 • All-cause mortality at Day 28 (proportion of subjects deceased) • Time to death from any cause at Day 28 • Change in PaO_2/FiO_2 ratio as categorical variable using Berlin criteria for ARDS categorization (mild, moderate, severe) (time range: Days 1 to 28) • Change in PaO_2/FiO_2 ratio as continuous variable (time range: Days 1 to 28) • Change in resting SpO_2 adjusted by FiO_2 (time range: Days 1 to 28) • Change in (non-invasive) oxygen supplementation requirements (time range: Days 1 to 28) **Safety Assessments:** Treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs), including hypersensitivity/ anaphylactic reactions; clinical laboratory parameters and vital signs.
STUDY DESIGN
This is a randomized, double-blind, placebo-controlled phase 2 study to evaluate the efficacy and safety of intravenous pamrevlumab, a monoclonal antibody against connective-tissue growth factor (CTGF), in hospitalized subjects with acute COVID-19 disease. Eligible subjects are those with documented SARS-CoV-2 infection, age 40 to 85 years, with evidence of respiratory compromise requiring hospital admission. This age range was chosen to enhance detection of potential clinical benefits in subjects at highest risk for developing severe COVID-19 disease in this proof-of-concept study. Approximately 130 subjects will be randomized in a 1:1 ratio to either pamrevlumab or placebo; all subjects will also receive standard-of-care in the judgment of the Investigator. Study drug administration is via IV infusion on Days 1 (day of randomization), 7, 14 and 28. A follow-up by visit will be performed 4 weeks after the last dose.

All concomitant medications, including approved and non-approved treatments for COVID-19 (e.g., hydroxychloroquine, IL-6 inhibitors, etc.), as well as supplemental oxygenation needs, will be collected and recorded. In addition, the following will be collected and recorded: documentation of SARS-Cov-2 infection, documentation of any other infection(s) prior to or during hospitalization, and whether or not aggressive care is withheld or withdrawn, including the reason for withholding or withdrawal of care (e.g., DNR/DNI order, resource limitation).

STUDY PERIODS

Screening Period: Up to 2 days prior to randomization

Treatment Period: 28 days

Follow-Up Period: 28 days after last dose

SUBJECT ELIGIBILITY CRITERIA

Inclusion Criteria:

1. Age 40-85 years
2. Confirmed SARS-CoV-2 infection by a FDA-authorized diagnostic test (e.g., polymerase chain reaction [PCR] or other approved assay from any specimen source; note: a positive serology/antibody test for SARS-CoV-2 does NOT qualify as evidence of acute COVID-19 disease)
3. Respiratory compromise requiring hospitalization for COVID-19 disease as evidenced by at least one (or more) of the following criteria:
   a. Interstitial pneumonia on CXR or HRCT (findings of consolidation or ground glass opacities), OR
   b. Peripheral capillary oxygen saturation (SpO_2) $\leq$ 94% on room air, OR
   c. Requiring non-invasive supplemental oxygen (e.g., nasal cannula, face mask) to maintain SpO_2
4. Not requiring mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) use at time of randomization
5. Agrees to not participate in another clinical trial for the treatment of COVID-19 disease through Day 28
6. Subject (or legally authorized representative) able to understand and sign a written informed consent form

Exclusion Criteria:

1. Female subjects who are pregnant or nursing
2. Participation in a clinical trial with another investigational drug for COVID-19 disease
3. Anticipated discharge from the hospital or transfer to another hospital or long-term care facility which is not a study site within 72 hours of randomization
4. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies

STUDY TREATMENT

Dose and mode of administration

Dose: 35 mg/kg IV

Dosing regimen: Days 1, 7, 14 and 28.

Other important information

Study drug should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies.

STATISTICAL METHODS

Determination of sample size

The sample size of 65 subjects in each treatment arm will provide approximately 80% power, at 10% two-sided significance level, to detect a 20% absolute difference in the proportion of subjects who never received mechanical ventilation / ECMO and are alive at Day 28. This assumes that 65% of subjects in the placebo arm that never received mechanical ventilation / ECMO and are alive at Day 28, compared to 85% in the pamrevlumab group.

Randomization

Subjects who meet all eligibility criteria during screening will be randomized in a 1:1 ratio (pamrevlumab vs placebo) centrally across all sites and based on a pre-determined randomization list from a permuted block design.

Statistical analysis methods

The analysis of the proportion of subjects who never received mechanical ventilation and/or ECMO and alive at Days 14 and Day 28, the proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28, proportion of subjects' clinical status based on an 8-point ordinal scale, and proportion of subjects with categorical PaO_2/FiO_2 ratio endpoints will be conducted using logistic regression model with treatment group and adjusting for relevant baseline prognostic covariates.

The number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, number of days on mechanical ventilation and/or ECMO at Day 28 will be analyzed using the analysis of covariance (ANCOVA).

Change in PaO_2/FiO_2 ratio to day 28, change in resting SpO_2 adjusted by FiO_2 to day 28, change in (non-invasive) oxygen supplementation requirements to day 28 will be analyzed using Mixed

Model for Repeated Measures (MMRM) approach using relevant prognostic factors as covariates and treatment and Time and treatment *time interaction.
The analysis will take into account the inter-current events as follows.

1. Treatment discontinuation (e.g., due to AEs, Withdrawal by Subject or Physician Decision): Missing endpoint will be imputed by the last result prior to discontinuation.
2. Death: Composite strategy: inter-current event is taken to be a component of the variable. For number of days not requiring mechanical ventilation at Day 14, number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, and number of days on mechanical ventilation and/or ECMO at Day 28; days with missing data after death will be imputed with the worst result until Day 28.
3. Treatment discontinuation due to recovering and discharged from hospital: Missing endpoint will be imputed with the last result prior to discontinuation.

Treatment comparison analysis of time to event endpoints, will be performed using cox regression model adjusting for relevant baseline prognostic factors. Hazard ratios together with 95% two-sided confidence intervals for the hazard ratio will be provided.

Time to recovery by Day 28, time to mechanical ventilation/ECMO or all-cause mortality by Day 28, and all-cause mortality at Day 28 (proportion of subjects deceased), and time to death from any cause at Day 28 will be analyzed using Cox regression adjusting for relevant prognostics factors. Other methods will be used as appropriate.

Safety analyses

All subjects who received any dose of pamrevlumab will be included in the safety population analyses which will summarize treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs), including hypersensitivity/ anaphylactic reactions; clinical laboratory parameters and vital signs.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents.

TABLE OF CONTENTS

2. INTRODUCTION

2.1. Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody that binds to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role (e.g, idiopathic pulmonary fibrosis, certain fibrotic cancers, and Duchenne muscular dystrophy [DMD]). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2. Background Information and Study Rationale

2.2.1. Connective Tissue Growth Factor (CTGF)

CTGF is a 38 kDa secreted matricellular glycoprotein of the cysteine-rich 61/CTGF/nephroblastoma overexpression family (Perbal, 2004, Rachfal, 2005) which was recently renamed cellular communication network (CCN) family (Perbal 2018). It is produced by many cells, including fibroblasts, myofibroblasts, endothelial cells, mesangial cells, and stellate cells.

CTGF is a central mediator of tissue remodeling and fibrosis (Lipson, 2012). CTGF is essential for the fibrotic activity of TGF-B (Mori, 1999, Wang, 2011) but it may also act independently of TGF-B. While much has been made of the role of TGF-B in fibrosis, studies of the role of fibronectin in pulmonary fibrosis showed that the activity of TGF-B is dependent on cellular fibronectin to induce myofibroblast differentiation and that cellular fibronectin may have a fundamental role in activation of latent TGF-B (Muro, 2008). Shi-wen and colleagues showed that critical activities of TGF-B in the fibrotic process are dependent on CTGF expression, including EMT and ECM deposition, supporting the idea that CTGF over-expression is critical for activities attributed to TGF-B (Shi-wen, 2006).

CTGF has been shown to be an important mediator of pulmonary fibrosis in a mouse model of bleomycin-induced pulmonary fibrosis (Bonniaud, 2004). Lasky and coworkers observed upregulation of CTGF messenger ribonucleic acid (mRNA) gene expression in a mouse model of bleomycin-induced pulmonary fibrosis, suggesting a possible role of CTGF in the pathogenesis of lung fibrosis (Lasky, 1998).

2.2.2. Study Rationale

Recent data indicate the presence of interstitial pneumonia (consolidation or ground glass opacities) in a subset of patients infected with novel coronavirus SARS-CoV-2 requiring hospitalization. The interstitial pneumonia is usually bilateral and responsible for reduced efficiency of gas exchange, potentially leading to respiratory failure, intubation and finally death in a significant proportion of patients requiring mechanical ventilation. CTGF (connective tissue growth factor; CCN2) may promote vascular leakage, and administration of pamrevlumab, an investigational anti-CTGF monoclonal antibody, can reverse edema. Using the Miles assay, CTGF promoted vascular leakage in skin (Data on file, generated by FibroGen). In rodent models of complications of diabetes, the abundance of CTGF in urine correlated to the extent of

albuminuria (Roestenberg et al. 2006; FibroGen Report 200_04_3050_034). Pamrevlumab was shown to inhibit vascular leakage in the lungs after irradiation (Bickelhaupt et al. 2017), and in several organs in complications of diabetes models (data on file at FibroGen), as well as to suppress ascites in a genetically engineered model of pancreatic cancer (Neesse et al. 2013). These observations suggest that administration of pamrevlumab may attenuate edema associated with the virus-induced pneumonia and improve gas exchange.

In addition, published data in several animal models (Pi et al. 2018; Bickelhaupt et al. 2017; Sternlicht et al. 2018; Makino et al. 2017; Booth et al. 2010) indicate that pamrevlumab alters trafficking of certain immune-related cells. In a mouse radiation-induced lung fibrosis (RILF) model, the mechanism by which pamrevlumab-treated mice experienced a rapid reversal of pneumonitis appears to be deactivation of myofibroblasts resulting in decreased secretion of inflammatory chemokines (Sternlicht et al. 2018). This hypothesis remains to be confirmed for the RILF model, and the mechanism(s) by which pamrevlumab alters immune cell trafficking remains to be determined. It should also be noted that none of these models involved active viral infections, so it is unclear if pamrevlumab would broadly affect inflammation associated with SARS-Cov-2 infection resulting in COVID-19 disease. However, if blocking CTGF attenuates inflammation, pamrevlumab might reduce symptoms associated with the virus-induced cytokine storm.

In addition to lung damage caused by the immune system's hyperactive attempt to eradicate the viral infection, invasive mechanical ventilation of ARDS patients may also contribute to development of pulmonary fibrosis (Cabrera-Benitez et al. 2014). In ARDS patients that developed fibrosis, there was a statistically significant correlation between ventilator settings and the abundance of TGFB and CTGF in serum (Xie et al. 2019). CTGF has been shown to be elevated in ventilated pre-term sheep, and to increase with gas volume (Wallace et al. 2009) and flow (Bach et al. 2008). CTGF expression also increases with tidal volume in neonatal rats (Wu et al. 2008). In ventilator-induced lung injury (VILI) models with adult rats, macrophages were reported to mediate disruption of epithelial barrier function and edema (Frank et al. 2006; Eyal et al. 2007). Interestingly, in the RILF model, macrophages represented the most enriched cell type induced by radiation damage, which were subsequently normalized by therapeutic pamrevlumab administration (Bickelhaupt et al. 2017; Sternlicht et al. 2018). Together, these data suggest that CTGF may mediate some aspects of ventilator-induced lung damage and that pamrevlumab may attenuate some of the damage.

Hyperoxia may also contribute to acute lung injury in intubated ARDS patients (Schwarz 2001). In the rat neonatal hyperoxia model of bronchopulmonary dysplasia, an antibody with activity similar to that of pamrevlumab was able to improve lung development in non-ventilated pups (Alapati et al. 2011). This suggests that pamrevlumab might attenuate some of the pathology associated with hyperoxia.

Pathophysiology resulting from SARS-Cov-2 may lead to interstitial lung fibrosis in patients that survive the infection. Data from a retrospective cohort study in Wuhan, China (Zhou F Lancet 2020; 395: 1054) show that more than one-third of COVID-19 patients surviving pneumonia have residual respiratory failure, due to fibrotic changes in the lung. Approximately 15-30% of patients hospitalized for COVID-19 develop acute respiratory distress syndrome (ARDS) (Wang et al. 2020; Chen et al. 2020; Huang et al. 2020). Patients that survive ARDS often develop

fibrosis within 3-4 weeks (Zapol et al. 1979), and the onset of fibrotic changes can begin as early as 36 hours after lung injury (Schwarz 2001). The distribution and composition of extracellular matrix (ECM) within the alveolar wall is similar in both ARDS and idiopathic pulmonary fibrosis (IPF) (Raghu et al. 1985), suggesting that pamrevlumab, which has demonstrated antifibrotic effects in IPF patients (Raghu et al. 2016; Richeldi et al. 2020), might help in reducing residual fibrotic damage in lungs of patients with COVID-19.

CTGF is a key mediator of pro-fibrotic pathways that has a very complicated biology (Lipson et al. 2012). Considered together, the data above suggest that its inhibition might mitigate interstitial fibrosis in the post-acute infection setting via multiple mechanisms. In addition, it might attenuate edema acutely associated with ARDS and VILI, which may improve gas exchange.

This clinical study has been prepared based on these rationales to address the current medical emergency, given the extremely high number of patients affected by COVID-19 disease.

2.3. Summary of Past Clinical Studies, Safety and Dosing Information

The clinical trial experience with pamrevlumab includes 11 completed clinical studies to date. A total of 624 subjects have received investigational drug and/or standard of care in these clinical trials, including 270 subjects with IPF, 112 subjects with pancreatic cancer, 21 pediatric subjects with DMD, 112 subjects with liver fibrosis secondary to hepatitis B, 107 subjects with DN, and 2 pediatric subjects with focal segmental glomerulosclerosis (FSGS). Approximately 530 subjects have received pamrevlumab across these clinical trials. There are studies currently ongoing in patients with IPF, pancreatic cancer, and DMD.

Adverse events (AEs) have been generally mild or moderate in severity and transient in duration. The AEs have been typical of the patients' underlying medical condition(s) and, in placebo-controlled studies, were equally distributed between the placebo and pamrevlumab treatment groups. Infusions of pamrevlumab have been well tolerated. There is no apparent pattern to the serious adverse events (SAEs) observed during clinical trials.

In a placebo-controlled Phase 2 IPF study of approximately 100 patients, pamrevlumab was well tolerated, with a safety profile similar to that of placebo. The placebo group reported more TEAEs of cough (43%) than in the pamrevlumab group (28%). TESAEs were observed in 12 patients (24%) in the pamrevlumab group and 8 (15%) in the placebo-group and were mostly respiratory-related; however, fewer patients in the pamrevlumab group discontinued study treatment because of a TESAE than did those in the placebo group., and fewer patients in the pamrevlumab group (5 [10%]) compared to placebo (7 [13%]) were hospitalized following a respiratory-related TESAE. Nine patients died during the study: three (6%) in the pamrevlumab group and sic (11%) in the placebo group.

A Phase 2 dose-response study of pamrevlumab was performed in pancreatic cancer patients (Picozzi et al. (2017) J Clin Cancer Trials 2:1). In this study, pamrevlumab (FG-3019) was administered every two weeks at doses up to 45 mg/kg, or weekly at 22.5 mg/kg after a loading dose of 45 mg/kg. Patients that had trough plasma levels of pamrevlumab immediately before the second dose that was greater than 150 µg/ml exhibited better overall survival than those whose plasma trough levels were less than 150 µg/ml. Patients that had ascites exhibited lower plasma levels of pamrevlumab than patients without ascites. This may be because ascites fluid

contains significant amounts of CTGF (data on file), and therefore may act as a sink for administered antibody. Patients with ascites that achieved high trough levels of pamrevlumab (>150 µg/ml) had a median overall survival that was about 4 times longer than those that had lower trough levels (8.7 vs. 1.9 months). Together, these data suggest that it is important to achieve high plasma exposure to pamrevlumab in order to achieve maximal benefit.

In a Phase 2 open label, study, randomized study in locally advanced unresctable pancreatic cancer LAPC), patients received 35mg/kg on days 1, 7 and 14 and then after every two weeks for total of six month in combination with gemcitabine and paclitaxel vs. combination of gemcitabine and paclitaxel. No safety concerns were seen with this dosing regimen and a phase 3 study in LAPC is ongoing.

In an open label study in patients age 12 and above with non-ambulatory Duchenne Muscular Dystrophy (DMD), pamrevlumab has been administered at 35mg/kg, every 2 weeks, for nearly two years with no safety concerns identified. Considered together, the data suggest that three weekly doses of pamrevlumab at 35 mg/kg, followed by bi-weekly administration for several more months should be well tolerated.

Supporting the dosing regimen of 35 mg/kg, dosed weekly until Day 14, followed by every 2 weeks for the remaining treatment period, are data from the PRAISE clinical trial. PRAISE was a phase 2 placebo-controlled study in IPF with administration of pamrevlumab once every three weeks at 30 mg/kg, for 48 weeks. In PRAISE, the rate of FVC loss in the pamrevlumab-treated group was indistinguishable from that of placebo for the first 12 weeks, after which the rate of loss in the pamrevlumab-treated subjects was significantly slower (Richeldi et al, 2019). This observation suggests that adequate exposure to pamrevlumab to manifest its activity in IPF patients was not achieved until about the 4^{th} or 5^{th} dose when it was administered at 30 mg/kg every 3 weeks. Repeat dose pharmacokinetic (PK) data in non-human primates indicates that achievement of steady-state levels of circulating pamrevlumab requires multiples doses, and that this is achieved faster at higher and more frequent doses. Computer modeling of pamrevlumab PK in humans also suggests that addition of at least one “loading dose” will result in more rapid achievement of efficacious plasma levels. This is the reason for the proposed dosing regimen in this acute-care setting.

Over the course of the entire study, there were numerically more subjects with a HAHA response in the pamrevlumab group than in the placebo group. During the main study randomized treatment period, 2 subjects in the placebo group had a sample that was both specific and reactive for antibodies to pamrevlumab. In the open-label extended treatment period, 7 subjects had samples that were specific and reactive: 2 subjects who were randomized to receive pamrevlumab and 5 subjects that were randomized to receiving placebo. In a sub-study, 2 subjects had specific and reactive samples, 1 subject in the pamrevlumab/pirfenidone group and 1 subject in the pamrevlumab/nintedanib group.

Overall, incidence of apparent HAHA within the group was low and the signal was detected at a low titer. Therefore FibroGen believes that these HAHA responses are most likely due to non-specific assay variability. However, FibroGen will continue to assess the impact of immunogenicity and neutralizing antibody (if any) in future studies.

In summary, pamrevlumab has been shown to be well tolerated. For additional information on the safety of pamrevlumab in IPF patients and in other indications, please refer to the current version of the Investigator's Brochure.

2.3.1. Clinical efficacy in completed studies:

Two studies of pamrevlumab in subjects with pancreatic cancer have demonstrated preliminary evidence of efficacy as measured by OS and by eligibility for surgical exploration and resection.

The results of an open-label Phase 2 study and a randomized, placebo-controlled Phase 2 study suggests pamrevlumab slows the progression of IPF as measured by change in FVC % predicted, quantitative analysis of fibrosis, and time to disease progression or death. (King 2009; Raghu et al, 2004; Zisman et al, 2010; King et al, 2014; Richeldi et al, 2014; Raghu et al. 2016, Clukers et al. 2018; Richeldi et al, 2019).

2.4. Ongoing clinical study in patients with SARS-CoV-2 Infection

An Investigator-Initiated Phase 2/3 open-label, randomized, parallel-arm study investigating the efficacy and safety of intravenous administration of pamrevlumab versus standard of care in patients with COVID-19 disease due to SARS-CoV-2 infection has recently been initiated in Italy: Study FGCL-3019-IST-014.

3. OBJECTIVES AND ASSESSMENTS

3.1. Objective

To assess the efficacy and safety of intravenous pamrevlumab, an investigational monoclonal antibody against connective-tissue growth factor (CTGF), compared to placebo, in hospitalized patients with acute COVID-19 disease due to confirmed SARS-COV-2 infection.

3.2. Efficacy Assessments

Primary Efficacy Endpoint

Proportion of subjects who never received mechanical ventilation and/or ECMO and alive at Day 28

Secondary Efficacy Endpoints

- Proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28
- Proportion of subjects who never received mechanical ventilation and/ or ECMO and alive at Day 14
- Time to recovery by Day 28 based on 8-point ordinal scale (Day of recovery is defined as the first day on which the patient satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen; 2) Not hospitalized (discharged), but with limitation on activities and/or requiring

home supplemental oxygen; 3) Not hospitalized (discharged), with no limitations on activities and not requiring supplemental oxygen

- Clinical status based on 8-point ordinal scale (time range: Days 1 to 28)
- Days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28
- Days on mechanical ventilation and/or ECMO at Day 28
- Time to mechanical ventilation/ECMO or all-cause mortality at Day 28
- All-cause mortality at Day 28 (proportion of subjects deceased)
- Time to death from any cause at Day 28
- Change in PaO_2/FiO_2 ratio as categorical variable using Berlin criteria for ARDS categorization (mild, moderate, severe) (time range: Days 1 to 28)
- Change in PaO_2/FiO_2 ratio as continuous variable (time range: Days 1 to 28)
- Change in resting SpO_2 adjusted by FiO_2 (time range: Days 1 to 28)
- Change in (non-invasive) oxygen supplementation requirements (time range: Days 1 to 28)

3.3. Safety Assessments

Treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs), including hypersensitivity/ anaphylactic reactions; clinical laboratory parameters and vital signs.

4. OVERALL STUDY DESIGN

This is a randomized, double-blind, placebo-controlled phase 2 study of the efficacy and safety of intravenous pamrevlumab, a monoclonal antibody against connective-tissue growth factor (CTGF), in hospitalized subjects with acute COVID-19 disease due to SARS-CoV-2 infection.

Eligible subjects are those with documented SARS-CoV-2 infection, age 40 to 85 years, with evidence of respiratory compromise requiring hospital admission. This age range was chosen to enhance detection of potential clinical benefits in subjects at highest risk for developing severe COVID-19 disease in this proof-of-concept study.

The total sample size is approximately 130 subjects. Subjects are randomized in a 1:1 ratio, according to a pre-determined randomization list from a permuted block design.

Study drug will be administered as IV infusion on Days 1 (day of randomization), 7, 14 and 28. A follow-up by visit will be performed 4 weeks after the last dose.

All subjects will be treated with standard-of-care according to the judgment of the Investigator. All concomitant treatments, including approved and non-approved therapies for COVID-19 disease, will be collected and recorded (see also Section 6.3).

Safety will be intensively monitored throughout the study. A detailed overview of collection of assessments is provided in Section 6 and Schedule of Assessments (SOA).

4.1. Subject ID Assignment

Subjects that sign consent will be assigned an 8 digit Subject ID number consisting of a four digit site number and a 4 digits Subject ID starting with 1xxx. Subject numbering will be assigned sequentially as subjects are recruited/screened (e.g., 1001, 1002, and 1003, etc.).

4.2. Randomization

Subjects who meet the eligibility criteria during screening will be randomized in a 1:1 ratio (pamrevlumab vs placebo) centrally across all sites.

Automated randomization and treatment assignments will be performed by an Interactive Response System (IXRS or IRT).

4.3. Blinding

This is a double-blind, placebo-controlled study. The Investigator, study site staff, subjects, selected sponsor clinical team and designees are blinded to study drug assignment. Blinded treatment with a placebo control is the gold standard method for obtaining unbiased assessments of safety and efficacy in clinical trials of investigational drugs such as pamrevlumab.

The study blind will be maintained for all parties specified above throughout the study. Pamrevlumab and placebo will be identical in appearance, packaging, and labeling in order to maintain the study blind.

4.3.1. Request for Unblinding of Treatment Assignment

Investigators, study site staff and subjects will remain blinded to treatment assignments until study completion and database lock.

Breaking the blind during the study (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator due to immediate safety concerns, or is considered essential for the immediate subject management, and should be discussed with the Medical Monitor beforehand, if possible. It is the responsibility of the investigator to promptly document and explain any unblinding to the sponsor.

4.4. Study Duration

The Screening Period is up to 2 days prior to randomization, to confirm eligibility.

The Treatment Period is 28 days. Study drug will be administered as IV infusion on Days 1 (day of randomization), 7, 14 and 28.

The Follow-Up Period is 28 days after the last dose.

Visits /assessments will occur every day for 28 days, or until hospital discharge, whichever occurs earlier. If a subject is discharged prior to Day 14 or Day 28, the subject should return as outpatient on Days 14 and/or Day 28, for study drug infusions and assessments. For subjects who cannot return for an in-person visit, study assessments maybe done remotely, such as via phone.

Subjects who discontinue study treatment prior to Day 28 are encouraged to remain in the study to complete all remaining visits and assessments, including for collection of vital status. Subjects

who discontinue treatment, for any reason, will need to return for an Early Treatment Discontinuation visit 28 days (+7 Days) after the last infusion and may be contacted by phone at Day 14 and 28 to check the subject's survival status.

See also Section 5 and 6 for additional detail.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

In order to be eligible for inclusion in this trial, a Subject must meet all of the following:

1. Age 40-85 years
2. Confirmed SARS-CoV-2 infection by a FDA-authorized diagnostic test (e.g., polymerase chain reaction [PCR] or other approved assay from any specimen source; note: a positive serology/antibody test for SARS-CoV-2 does NOT qualify as evidence of acute COVID-19 disease)
3. Respiratory compromise requiring hospitalization for COVID-19 disease as evidenced by at least one (or more) of the following criteria:
4. Interstitial pneumonia on CXR or HRCT (findings of consolidation or ground glass opacities), OR
5. Peripheral capillary oxygen saturation (SpO_2) $\leq$ 94% on room air, OR
6. Requiring non-invasive supplemental oxygen (e.g., nasal cannula, face mask) to maintain SpO_2
7. Not requiring mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) use at time of randomization
8. Agrees to not participate in another clinical trial for the treatment of COVID-19 disease through Day 28
9. Subject (or legally authorized representative) able to understand and sign a written informed consent form

5.2. Exclusion Criteria

Subjects will be excluded from this trial if any of the following apply:

1. Female subjects who are pregnant or nursing
2. Participation in a clinical trial with another investigational drug for COVID-19 disease
3. Anticipated discharge from the hospital or transfer to another hospital or long-term care facility which is not a study site within 72 hours of randomization
4. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies

5.3. Early Treatment Termination and Study Withdrawal

Subjects who do not receive all study drug doses are encouraged to remain in the study and continue with the regular study visits and assessments. However, subjects may withdraw from the study at any time, for any reason. Reasons for discontinuing study drug treatment, as well as reasons for withdrawing from study, will be captured on CRF.

Subjects are encouraged to have a final follow-up visit (in person or remotely, such as by phone) to check on vital status and general health of the subject. Vital status may also be obtained from public records.

Reasons for terminating treatment early may include:

- Any safety concern in the Investigator's opinion, that precludes further study participation
- Female subjects who are pregnant or nursing
- Participation in a clinical trial with another investigational drug for COVID-19 disease

Mandatory reasons for withdrawing the subject from the study include:

- Withdrawal of Consent
- Lost To Follow-Up

5.4. Replacement of Study Subjects

All randomized subjects will be included in the study. Subjects who terminate the study early will not be replaced.

5.5. Study Closure

FibroGen reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of the study site or termination of the study by FibroGen may include (but are not limited to):

- Successful completion of the study at the investigational site
- The required number of subjects for the study has been recruited
- Failure of the Investigator to comply with the protocol, GCP guidelines or local requirements
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

6. STUDY ASSESSMENTS

6.1. Laboratory Assessments, including ABG and SpO2

Labs will be collected locally for safety and include hematology: CBC (complete blood count) and differential, chemistry: CMP (Comprehensive Metabolic Panel), and routine coagulation panel (INR, PT, aPTT).

Arterial blood gas (ABG) will be collected each day the patient is in ICU/CCU, and recorded anytime if performed as part of routine care outside ICU/CCU, while hospitalized.

Peripheral capillary oxygen saturation (SpO2) will be collected each day while hospitalized.

6.2. Modified WHO Ordinal Scale

Assessment of clinical status, using an 8-Point, Modified WHO Ordinal Scale as specified below, should be assessed daily, until Day 28:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitations on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen, no longer requiring medical care
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19-re;ated or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, requiring nasal high-flow oxygen, non-invasive mechanical ventilation, or both
7. Hospitalized, requiring invasive mechanical ventilation, extra-corporeal membrane oxygenation (ECMO), or both
8. Death

6.3. Concomitant Medications, Supplemental Oxygen Needs, and other Care

Subjects will be treated according to best available standard-of-care according to the judgment of the Investigator. All concomitant medications, including approved and non-approved treatments for COVID-19 (e.g., hydroxychloroquine, IL-6 inhibitors, etc.), as well as supplemental oxygen needs, will be collected and recorded.

In addition, the following will be recorded and collected: documentation of SARS-Cov-2 infection, documentation of any other infection(s) prior to or during hospitalization, and whether or not aggressive care is withheld or withdrawn, including the reason for withholding or withdrawal of care (e.g., DNR/DNI order, resource limitation). Vital status may also be obtained from public records.

7. STUDY DRUG

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF and is formulated as solution for administration by IV infusion.

Pamrevlumab is supplied in single-use glass vials containing sterile, preservative-free solution (100 mg pamrevlumab/vial or 500 mg pamrevlumab/vial respectively). The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL L-histidine, 3.08 mg/mL L-histidine HCl, 8.01 mg/mL sodium chloride, and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

Matching placebo is formulated as solution to be administered in a manner that is identical to pamrevlumab infusion.

7.1. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice requirements for labelling and local regulatory guidelines.

7.2. Study Drug Storage

Study drug vials must be stored refrigerated (2°C to 8°C), in a temperature- controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation. Details regarding the reporting of temperature excursions can be found in the study Investigational Product (IP) Manual.

7.3. Study Drug Preparation

Study drug is infused undiluted after pooling the contents of the calculated number of vials in an empty infusion bag (total volume of fluid must not exceed **410 mL**) according to the Dose Preparation Instructions in the IP Manual.

Study drug solutions for infusion must be stored refrigerated (2°C to 8°C) and administered within 24 hours of preparation and administered within 6 hours of stored at room temperature. Study drug infusion solutions are administered by IV infusion, using an infusion set with a 0.2 µm in-line filter.

7.4. Study Drug Administration

Dosing will be based on the weight obtained on Day 1. The total dose **is not to exceed 4.1g**. The dose should be prepared in a **volume of fluid that does not exceed 410 mL**. Study drug will be administered as soon as possible after release from the site's pharmacy and infused within 24 hours of preparation. Study drug will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

The first infusion shall be completed in approximately 2 hours. If the first infusion is well tolerated and no infusion related AEs are observed during the infusion or subsequent 1-hour observation period, the second infusion shall be completed in approximately 1 hour. The 2

subsequent infusion periods may be shortened to approximately 30 minutes if no infusion-related AEs were observed.

If an infusion-related AE occurs during the subsequent infusion, study drug will be administered over approximately 1 hour for the next three infusions. If no drug-related AEs are observed in any of these three infusions, the duration of infusion may be decreased to approximately 30 minutes.

The Investigator or other qualified personnel must be either present, or immediately available, during all infusions and observation periods for each Subject. If a Subject has a significant infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms.

Medications for the treatment of acute reactions, including anaphylaxis, must be available to study site staff for immediate use. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

7.5. Study Drug Handling and Disposal

All study drug must be controlled and tracked. Drug accountability and reconciliation for all study drug received should be completed by the study site. All used, unused, and partially used study drug should be destroyed on site according to local/institutional policies by the pharmacy/authorized staff with approval from Sponsor (or designee), and destruction records maintained. IV bags used to infuse study drug can be disposed of per institutional policy.

8. ASSESSMENTS OF SAFETY

8.1. Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the study drug.

8.2. Definitions

8.2.1. Definition of an Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject as defined in the study protocol are recorded in the subject's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or

involves an intervention, such as elective cosmetic surgery, or a medical procedure while on study, is not considered an adverse event.

8.2.2. Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the primary cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be a SAE.

Scheduled or pre-planned hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures (including elective procedures) do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1. Adverse Event Reporting Period

The safety reporting period begins after the subject has signed the informed consent and ends 28 days after the last dose of study drug. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5). Pregnancy reporting requirements are outlined in Section 8.3.6.

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will actively seek information from each subject at each visit to collect any AEs occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit. There will be no directed questioning for any specific AE. This does not deter the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The investigator is expected to follow reported adverse events until stabilization or reversibility.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the most current National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE v5.0) guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g.,

preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.

- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death**: Fatal AE.

8.3.4. Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile of the study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- Related:
  - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- Not Related:
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5. Reporting Serious Adverse Events (SAEs)

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through 28 days after the last dose of pamrevlumab are recorded in the subject's medical record and are submitted to FibroGen. All SAEs must be submitted to FibroGen within 24 hours following the investigator's knowledge of the event via the SAE report form. Additionally, pamrevlumab related SAEs (including deaths) that occur after the EOS/safety follow-up visit will be reported.

If a subject is permanently withdrawn from protocol required therapies because of a serious adverse event, this information must be submitted to FibroGen. FibroGen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and central IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

8.3.5.1. Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations and IRB/EC requirements. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2. Deaths

The investigator will report the fatal event to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.4.

If the death occurred within the AE collection and reporting period (signed ICF to 28 days after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. If the investigator becomes aware of a

death occurring after the AE reporting period and considers it related to pamrevlumab, it will be reported as an SAE.

8.3.6. Pregnancies: Reporting and Follow-up of Subjects and Female Partners of Subjects

The outcome of all pregnancies for female subjects or female partners of male subjects should be followed up and documented as described. If a female subject or a female partner of a male subject becomes pregnant while the subject is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to the Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

Pregnancy itself is not an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the subject was discontinued from the study. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If a lactation case occurs while the female subject is taking protocol-required therapies, or within 28 days after the last dose of study treatment, report the lactation case to FibroGen. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the last dose of pamrevlumab. Any lactation case should be reported to FibroGen's Safety within 24 hours of the investigator's knowledge of event.

8.3.7. Laboratory or other Test Abnormalities/ Findings

All new or worsened laboratory abnormalities should be reported as AEs. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8. Hypersensitivity/Anaphylactic Reactions:

Hypersensitivity and anaphylactic reactions will be monitored throughout the study, using the criteria below as defined per Sampson et al. 2006 (Sampson, 2006).

Anaphylaxis is highly likely when the following criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

And at least one of the following criteria:

a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

8.3.9. Safety Monitoring

Safety will be assessed throughout the study. A medically complete baseline profile of each subject will be established through medical history, a complete physical examination including vital signs, laboratory tests and PFTs. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Safety and tolerability will be monitored closely by FibroGen.

8.3.9.1. Special Reporting Situations

Special Reporting Situations on FibroGen investigational product Pamrevlumab that require safety evaluation include:

- Overdose (any dose greater than 4.1g)
- Suspected abuse/misuse
- Inadvertent or accidental exposure
- Medication error (e.g. incorrect dose administered)
- Drug-drug interactions

Report special situations to FibroGen’s Safety within 24 hours of the investigator’s knowledge of the event. See Study Reference Manual for detailed reporting instructions.

8.3.9.2. Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (DMC) will be utilized and will be composed of external experts. Composition and responsibilities of the DMC will be defined in a separate DMC charter. The DMC responsibilities will include an interim analysis for safety, in accordance with the DMC Charter and an Interim Analysis Plan.

9. STATISTICS

9.1. Sample Size Determination

The sample size of 65 subjects in each treatment arm will provide about 80% power, at 10% two-sided significance level, to detect a 20% difference in the proportion of subjects who never received mechanical ventilation / ECMO and alive at Day 28. This assumes that 65% of subjects in the placebo arm who never received mechanical ventilation and/or ECMO at Day 28, compared to 85% in the pamrevlumab group.

9.2. Analysis Populations

Enrollment and disposition summaries will be provided on all randomized subjects.

The Safety Population consists of all subjects who have received at least one dose of study drug. All safety summaries will be based on the Safety Population.

The Intent-To-Treat Set (ITT) consists of all randomized subjects. All efficacy analyses will be performed based on the ITT set.

9.3. General Considerations

Baseline value is defined as mean of all screening and Day 1 values prior to the first dose.

Descriptive summaries will be presented for study parameters including baseline characteristics, safety, and efficacy.

Continuous variables will be reported in mean, standard deviation or standard error, median, Q1-Q3, minimum, and maximum.

Categorical variables will be reported in frequency and percentage of subjects within each outcome category.

9.4. Statistical Methods

The analysis of the proportion of subjects who never received mechanical ventilation and/or ECMO and are alive at Days 14 and 28, the proportion of subjects alive, discharged home, and not on supplemental oxygen at Day 28, proportion of subjects' clinical status based on an 8-point ordinal scale, and proportion of subjects with categorical PaO_2/FiO_2 ratio endpoints will be conducted using logistic regression model with treatment group and adjusting for relevant baseline prognostic covariates.

The number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, number of days on mechanical ventilation and/or ECMO at Day 28 will be analyzed using the analysis of covariance (ANCOVA).

Change in PaO_2/FiO_2 ratio to day 28, change in resting SpO_2 adjusted by FiO_2 to day 28, change in (non-invasive) oxygen supplementation requirements to day 28 will be analyzed using Mixed Model for Repeated Measures (MMRM) approach using relevant prognostic factors as covariates and treatment and Time and treatment *time interaction

The analysis will take into account the inter-current events as follows.

1. Treatment discontinuation (e.g., due to AEs, Withdrawal by Subject or Physician Decision): Missing endpoint will be imputed by the last result prior to discontinuation.
2. Death: Composite strategy: inter-current event is taken to be a component of the variable. For number of days not requiring mechanical ventilation at Day 14, number of days in ICU/CCU (either on or off mechanical ventilation and/or ECMO) at Day 28, and number of days on mechanical ventilation and/or ECMO at Day 28; days with missing data after death will be imputed with the worst result until Day 28.
3. Treatment discontinuation due to recovering and discharged from hospital: Missing endpoint will be imputed with the last result prior to discontinuation.

Treatment comparison analysis of time to event endpoints, will be performed using cox regression model adjusting for relevant baseline prognostic factors. Hazard ratios together with 95% two-sided confidence intervals for the hazard ratio will be provided.

Time to recovery by Day 28, time to mechanical ventilation/ECMO or all-cause mortality by Day 28, and all-cause mortality at Day 28 (proportion of subjects deceased), and time to death from any cause at Day 28 will be analyzed using Cox regression adjusting for relevant prognostics factors. Other methods will be used as appropriate.

9.5. Safety Analyses

All subjects who received any dose of pamrevlumab will be included in the safety analyses which will summarize treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs); clinical laboratory parameters and vital signs, as well as hypersensitivity/anaphylactic reactions.

10. ETHICS

10.1. Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirements, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

This protocol, the Informed Consent Form, and the Investigator's Brochure must be approved by a properly constituted IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator.

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

Prior to participation in any study-specific procedures, the subject (or legally authorized representative) must sign an IRB/IEC-approved written Informed Consent Form (ICF) in his/her native language.

10.2. Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining re-approval by the IRB/IEC annually or as required by the policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required reports submitted to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen or designee. A copy of the signed FDA Form 1572 or other qualified investigator statement (as required) must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen or its designee. Written documentation of IRB/IEC approval must be received before the amendment is implemented.

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

10.3. Subject Information and Consent

Prior to participation in any study-specific procedures, the subject must sign (note: all references to "subject" in this section refers to the study subject or his/her legally acceptable representative) an IRB/IEC-approved written Informed Consent Form (ICF) in his/her native language. The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the subjects. To obtain and document informed consent, the Investigator should comply with applicable regulations, and adhere to ICH GCP standards.

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and IRB/IEC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of the signed and dated ICF.

If there are any changes to the IRB/IEC approved ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF, if/as required by the IRB/IEC.

Each subject (or legally authorized representative) must provide his or her consent for the use and disclosure of personal health information in accordance with applicable regulatory requirements.

10.4. Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent or other disclosure authorization documents signed by the subject, unless permitted or required by applicable law.

11. DATA HANDLING AND RECORD KEEPING

11.1. Source Documents

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. The investigator or designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the Case Report Forms (CRFs) and resolved queries.

11.2. Direct Access to Source Documents

The investigator must provide direct access to source data and source documents for trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspection. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information and medical records.

11.3. Data Collection, Handling, and Verification

All required data will either be entered onto CRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data (i.e. CRFs and queries) throughout the duration of the study and prior to study completion, ensuring that all data are verifiable with source documents.

11.4. Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, FibroGen, and to the regulatory authorities, if required.

11.5. Retention of Data

A FibroGen representative will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or FibroGen or designee, the Investigator agrees to keep records, including the identity of all participating subjects (eg, subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of drug disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the Investigator may need to retain these documents for a longer period if required by applicable law, regulatory requirements or by an agreement with FibroGen whichever is longer.

11.6. Financial Disclosure

The Investigator’s disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The Investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 or other qualified investigator statement must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study. The Investigator Financial Disclosure Form for any Investigator(s) leaving the clinical site prior to study completion will be obtained prior to study completion.

12. PUBLICATION POLICY

The data and results of the study will be owned solely by FibroGen and shall be confidential information of FibroGen, subject to the Investigator's publication rights, described below and if any outlined in the Clinical Trial Agreement. It is understood by the Investigator that FibroGen may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators, the

Licensing Authority or to regulatory agencies of other governments. To allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to FibroGen.

Any publication or presentation of the results of this clinical study by the Investigator may only be made in strict compliance with the provisions of the Clinical Trial Agreement. Any publication relating to the study shall be made in collaboration with FibroGen. The Investigator should understand that it is not FibroGen's intention to prevent publication of the data generated in the clinical study. However, FibroGen reserves the right to control the form and timing of such publication for commercial reasons. The Study Center and Investigator shall adhere to the publication language as outlined in both Clinical Trial Agreement and the protocol to the extent that if there is any conflict or ambiguity between Clinical Trial Agreement and the protocol, the publication terms in the Clinical Trial Agreement shall prevail.

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APPENDIX 1: SCHEDULE OF ASSESSMENTS	**Screening**	**Treatment [7]**							**4-Weeks after Last Dose[7]**
	Up to 2 days prior to Day 1	Day 1	Days 2-6[6]	Day 7	Days 8-13[6]	Day 14[8]	Days 15-27 [6]	Day 28[8]	
Informed consent	X								
Eligibility criteria	X								
Medical History	X								
Demographic information	X								
Vital signs	X	X[1]	X	X[1]	X	X[1]	X	X[1]	
Urine pregnancy test[2]	X								
Concomitant medication and non-drug therapies	X	X	X	X	X	X	X	X	X
Infusion		X		X		X		X	
Local laboratory tests (hematology: CBC and differential, chemistry: CMP, coagulation parameters: INR, PT, aPTT)		X		X		X		X	X
Arterial Blood Gasses (ABG) [5]	X	X	X	X	X	X	X	X	
Resting SpO2 [4]	X	X	X	X	X	X	X	X	
Oxygen Supplementation Needs[3, 4]	X	X	X	X	X	X	X	X	
WHO Ordinal Scale		X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X
Survival, ICU and Hospital Discharge Status		X	X	X	X	X	X	X	X

[1] On infusion days, vitals taken within 30 minutes prior and 30 min after infusion; otherwise vitals taken daily [2] Women of child-bearing potential.
[3] Need for mechanical ventilation/ECMO, including ventilator settings, or supplemental oxygen, including mode of oxygen delivery. [4] Collected until Day 28 or hospital discharge, whichever occurs earlier [5] ABGs are collected daily while in ICU/CCU, and recorded if performed as part of routine care outside of ICU/CCU, until Day 28 or hospital discharge, whichever occurs earlier [6] if subject is discharged, these visit do not apply; subject should return for infusion visits only. [7] If a subject is discharged from hospital before Day 28, and unwilling to return for visits and infusions in an outpatient setting, visits may be conducted remotely for assessment of vital status and safety. If a subject is lost to follow-up after hospital discharge, vital status may also be obtained from public records. [8] Visit windows, for outpatient dosing visits ONLY: visit window for Day 14: +/- 2 days. Visit window for Day 28: +/- 3 days.