# AN 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

Final Protocol Number: FibroCov-01 / FGCL-3019-IST-014

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Type of Study: Phase 2/3

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**INVESTIGATOR INITIATED STUDY PROTOCOL**

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Location, date: Rome, 28th April 2020

***Confidential***

## 1. STUDY IDENTIFIERS

### 1.1. Title of study

An 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.

### 1.2. Clinical study number

FibroCov-01 / FGCL-3019-IST-014.

### 1.3. Sponsor

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### 1.4. Study sites

Fondazione Policlinico Universitario A. Gemelli IRCCS; Istituto Nazionale per le Malattie Infettive L. Spallanzani, Rome, Italy.

### 1.5. Type of study

Investigator Initiated Trial - Phase 2/3.

### 1.6. Study rationale

Recent data, including those from Italian hospitals, indicate the presence of interstitial pneumonia 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. Data on file, generated by FibroGen, suggest that CTGF (connective tissue growth factor; CCN2) may promote vascular leakage, and administration of pamrevlumab, an anti-CTGF monoclonal antibody, can reverse edema. This suggests that administration of pamrevlumab may improve gas exchange by attenuating edema associated with the virus-induced pneumonia.

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 radiation-induced lung fibrosis (RILF) model, the mechanism by which a rapid reversal of pneumonitis occurs appears to be via pamrevlumab deactivation of myofibroblasts that decreases their secretion of 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. However, if blocking CTGF attenuates inflammation, pamrevlumab might reduce symptoms associated with the virus-induced cytokine storm.

Finally, pathophysiology resulting from SARS-Cov-2 may lead to interstitial lung fibrosis in patients that survive the infection. CTGF is a key mediator of pro-fibrotic pathways and its inhibition might mitigate interstitial fibrosis in the post-acute infection setting. Data from a retrospective cohort study in Wuhan, China (Zhou et al. 2020) show that more than one third of COVID-19 patients surviving pneumonia have a residual respiratory failure, due to the presence of fibrotic changes in the lung. The well documented anti-fibrotic effects of pamrevlumab (Richeldi et al. 2019) might help in reducing the fibrotic residual damage in the lung of patients with COVID-19.

In addition to lung damage caused by the immune system's attempt to eradicate the viral infection, 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 mechanical power and the abundance of TGFβ and CTGF in serum (Xie et al. 2019). CTGF has been shown to be elevated in ventilated preterm 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). Together, these data suggest that CTGF may mediate some aspects of ventilator-induced lung damage. Hyperoxia may also contribute to acute lung injury in intubated ARDS patients (Schwarz et al. 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.

A Phase 2 dose-response study of pamrevlumab was performed in pancreatic cancer patients (Picozzi et al. 2017). 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 unresectable pancreatic cancer (LAPC), patients received 35 mg/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 35 mg/kg, every 2 weeks, for nearly two years with no safety concerns identified. A phase 3 study in LAPC is ongoing, and a phase 3 in non-ambulatory DMD is starting in the second quarter of 2020. 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 30 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 4th or 5th 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.

This protocol has been prepared based on these rationales to address the current medical emergency, given the extremely high number of patients affected by COVID-19. The objective of this study is to investigate a novel anti-CTGF therapeutic to reduce the number of patients requiring mechanical ventilation. This is intended to address the most urgent need to preserve access to intense care unit support and to potentially reduce mortality.

## 2. STUDY OBJECTIVES

### 2.1. Primary objective

The primary objective of this study is to assess the effect of pamrevlumab on relevant clinical parameters in COVID-19 patients requiring hospitalization.

### 2.2. Secondary objective

The secondary objective of this study is to evaluate the safety and tolerability profile of pamrevlumab in COVID-19 patients requiring hospitalization.

### 2.3. Exploratory objective

An exploratory objective of this study is to assess the long-term effect of pamrevlumab on lung fibrosis in patients with SARS-CoV-2 infection requiring hospitalization.

## 3. STUDY ENDPOINTS

### 3.1. Primary endpoint

Proportion of patients not on ventilatory support $\leq$15 days.

### 3.2. Futility testing

Futility testing will be performed when 23 pamrevlumab patients completed 14 days of treatment. For futility testing of Stage 1 of the study, a responder rate definition will be evaluated. Patients randomized to receive pamrevlumab are considered responders if the total number of days on mechanical ventilation is $\leq$15 days after first dose of pamrevlumab and the patient is alive.
In addition, chest high-resolution CT (HRCT) scans obtained at baseline and day 14 will used as supportive analyses in the assessment of futility. Such analyses will be based on both quantitative and qualitative changes by an independent imaging group.

### 3.3. Secondary endpoints

3.3.1. $PaO_2/FiO_2$ ratio as categorical variable: mild 200 mmHg < $PaO_2/FIO_2$ ≤ 300 mmHg; moderate 100 mmHg < $PaO_2/FIO_2$ ≤ 200 mmHg; severe $PaO_2/FIO_2$ ≤ 100 mmHg.

3.3.2. For patients already on mechanical ventilator at time of randomization, the number of days on ventilator after randomization.
3.3.3. For patients not on mechanical ventilator at time of randomization, the number of days not requiring invasive mechanical ventilation (i.e., ventilator-free days).
3.3.4. $PaO_2/FiO_2$ ratio as continuous variable.
3.3.5. Resting $SpO_2$ adjusted by $FiO_2$.
3.3.6. Change in oxygen supplementation requirements.
3.3.7. Quantitative and qualitative assessment of pulmonary lesions by chest HRCT scans at baseline and at day 14 and week 12.
3.3.8. Time to hospital discharge.
3.3.9. Time to all-cause mortality up to 28 days.
3.3.10. Proportion of patients discharged from ICU and alive within 28 days.
3.3.11. Proportion of patients alive within 28 days.

### 3.4. Safety endpoints

Safety endpoints will be:

1.3.4.1. Treatment-emergent adverse events and serious adverse events.
1.3.4.2. Treatment-emergent adverse events leading to premature discontinuation of study treatment.
1.3.4.3. Hypersensitivity reactions including anaphylactic/anaphylactoid reactions.
1.3.4.4. Treatment-emergent laboratory abnormalities
1.3.4.5. Assessment of immunogenicity.

## 4. STUDY DESIGN AND METHODS

### 4.1. Study design

This is a randomized, open-label, parallel-arm study to investigate the efficacy and safety of pamrevlumab in patients with documented SARS-CoV-2 infection. The study consists of screening, a treatment period, and a follow-up period.
The study will enroll patients who have been hospitalized and who are not currently on invasive mechanical ventilation. The treatment period is open ended, and patients will be randomized to treatment with pamrevlumab or standard of care in a 1:1 ratio according to a pre-generated randomization list. Pamrevlumab dosing, 30 mg/kg IV, will be administered at day 1, day 7 and day 14. Day 1 is defined as the day of randomization which must also include administration of the first dose of pamrevlumab for patients in the active treatment arm.
Based on Investigator's decision, treatment may be continued every 3 weeks after day 14, up to 11 weeks.
Since the treatment scheme of pamrevlumab for this study is more intense as compared to previous studies conducted in IPF patients, as a further safety measure the first 3 patients randomized to receive the experimental drug will be treated one at a time, leaving a 1-week observation period between them.
A follow-up by visit or phone call will be performed 8 and 12 weeks after the end of the last dose of treatment. The treatment period for an individual patient will not exceed 11 weeks. The end of the study is defined as last patient last follow-up visit/phone call.
The study design has a total sample size of approximately 68 patients and consists of two stages. At the end of Stage 1 (Stage 1 requires 23 patients on pamrevlumab treatment arm), analyses of efficacy and safety will take place with a potential to stop the study for futility or for efficacy. A data

review committee composed of experts in respiratory medicine and intensive care will be involved in study oversight and interpretation of the study results. In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator is free to introduce any therapy considered necessary.

### 4.2. Number of subjects

The study will enroll approximately 68 patients. The study will first enroll approximately 50 patients in Stage 1 and may continue to enroll more patients after review of Stage 1 data.

### 4.3. Diagnosis and main criteria for inclusion

Eligible patients are those with documented COVID-19, age ≥18 to ≤80 years with interstitial pneumonia (findings of consolidation or ground glass opacities as assessed by chest HRCT) and respiratory distress, defined as $PaO_2/FiO_2$ ratio of ≥100 ≤300 mmHg, requiring supplemental oxygen and hospitalization.
Exclusion criteria for the study are the following:

- Invasive mechanical ventilation at screening;
- Pregnancy;
- Incapacity to express a valid informed consent;
- Known hypersensitivity to monoclonal antibodies used as experimental drugs for any clinical indication.

### 4.4. Background therapy

All patients enrolled in the study will receive background therapy according to standard clinical practice (including antimicrobial, prophylactic, and best supportive care therapies as deemed appropriate by the Investigator), excluding investigational drugs. Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, IV parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatments, ultrafiltration or hemodialysis, as well as general supportive care are permitted.

### 4.5. Concomitant and prohibited therapy

Patients previously treated with tocilizumab can be enrolled in the study, if considered not benefitting from the treatment, in the opinion of the Investigator.
Concomitant use of IL-1 inhibitors (e.g., anakira, canakinumab), TNF inhibitors, JAK inhibitors, and chloroquine/hydroxychloroquine is not allowed. If any of these therapies are initiated at the discretion of the Investigator (e.g., as rescue therapy due to worsening of the patient's condition), then the patient should be withdrawn from study.

### 4.6. Determination of sample size

This study's sample size is based on Simon's two-stage design (Simon, 1989) on the pamrevlumab arm. For futility testing of Stage 1 of the study, a responder rate definition will be evaluated. Patients randomized to receive pamrevlumab are considered responders if the total number of days on ventilation is ≤15 days after first dose of pamrevlumab and the patient is alive.
Key assumptions for sample size calculation include the following: (1) type I error rate, α (one-sided): 0.05; (2) power: 90%; (3) response probability of standard of care: 40%; (4) response probability of standard of care + pamrevlumab: 65%.
The null hypothesis that the true response rate is 40% will be tested against a one-sided alternative. In Stage 1, 23 patients will be accrued in pamrevlumab arm. If there are 9 or fewer responses in

these 23 patients, the study may be stopped. Otherwise, 11 additional patients will be accrued for a total of 34 in pamrevlumab treatment group. The null hypothesis will be rejected if 18 or more responses are observed in 34 patients on the pamrevlumab arm. This design yields a type I error rate of 0.05 and power of 90% when the true response rate is 65%.
The study will enroll approximately 50 patients in Stage 1 who will be randomized in 1:1 fashion (pamrevlumab vs. standard of care).

### 4.7. Statistical methods

For futility testing in Stage 1, a responder rate definition will be used. Patients randomized to receive pamrevlumab are considered responders if the total number of days on ventilation is $\leq$15 days after the first dose of pamrevlumab. In addition, chest HRCT scans obtained at enrollment and day 14 $\pm$ 2 will used as supportive analyses in the assessment of futility.
Analysis of continuous endpoints will be conducted using analysis of covariance (ANCOVA) model with baseline value as a covariate and relevant baseline prognostic factors as other covariates.
Analysis of categorical endpoints will be conducted using either Fishers Exact test or Cochran-Mantel-Haenszel test comparing the categories between the two treatment arms.
Analysis of the time to mechanical ventilation, time to all-cause mortality, and time to hospital discharge, respectively, will be undertaken by plotting Kaplan-Meier curves. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 95% two-sided confidence intervals. Other statistical methods will be applied, as appropriate.

## 5. Subject withdrawal criteria

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.

Reasons for withdrawing the subject from the study may include the following:

5.1. Any safety concern in the Investigator's opinion, that precludes further study participation
5.2. Pregnancy
5.3. Withdrawal of Consent

## 6. Pamrevlumab: storage, preparation and use

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 10 mg/ml pamrevlumab. 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.
Vials of pamrevlumab 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.
Pamrevlumab 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)

Pamrevlumab must be stored refrigerated (2˚C to 8˚C) and administered within 24 hours of preparation. Pamrevlumab or placebo infusion solutions are administered by IV infusion, using an infusion set with a 0.2 µm in-line filter.
Dosing will be based on the weight. The total dose of study drug is not to exceed 4.1g. Study Drug will be administered within 24 hours of preparation if stored 2˚C-8˚C or within 6 hours if stored at room temperature. 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).
Before and after each infusion vitals and AE assessments will be completed. The first 3 study drug infusions will last approximately 2 hours in duration. If the first 3 infusions are well tolerated, all other infusions will be shortened to 60 minutes in duration. Vital signs and assessment of AEs, including any symptoms of hypersensitivity and anaphylactic reactions, will be observed as follows: 2 hours after the first 3 infusions, followed by 1 hour, if the first 3 infusions were well tolerated.
If a patient experiences a hypersensitivity or anaphylactic reaction, the infusion should be immediately stopped; such a patient should be discontinued from further treatment, and followed for safety, up to 4 weeks after the last infusion.
All study drug is provided by FibroGen. All used and unused vials should be accounted for and drug accountability documentation will be maintained. Used and unused vials can be discarded. Records of destruction will be maintained.

## 7. Safety

All AEs observed or reported spontaneously during the course of the study will be recorded. Reports of hypersensitivity and anaphylactic reactions will be carefully monitored, including by the FibroGen Drug Safety department, as well as by an independent Data and Safety Monitoring Board (DSMB), as soon as it is assembled. 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 following attributes must be assigned to each AE:

7.1. Description (Investigator's verbatim term describing the event)
7.2. Dates of onset and resolution
7.3. Severity
7.4. Relationship to study drug
7.5. Outcome
7.6. Action taken regarding study drug
7.7. Other treatment required
7.8. Determination of "seriousness"

To date over 600 patients are exposed to pamrevlumab, few with IPF up to five years, and others for more than 4 years with non-ambulatory Duchenne Muscular Dystrophy. As of to-date, no treatment-emergent serious adverse events of allergic or anaphylactic reactions were observed. However, the study drug will be stopped and study terminated if signs of serious allergic reactions are observed.
Blood-samples to determine immunogenicity: human-anti-human antibodies (HAHAs) will be collected prior to first dose, at regular intervals: days 7 and 14 during treatment, as well as at the last visit, 12 weeks after the end of treatment, as part of safety analyses.

## 8. Data collection, handling, and verification

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. All required data will be entered onto source documents by authorized site personnel and all data including lab reports will be provided to FibroGen to be entered into a validated, clinical database compliant with 21 CFR Part 11 regulations.

### 8.1 Subject numbering

Subjects will be assigned an 8 digits subject ID number consisting of a four digits site number (2520) 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.). The first subject enrolled will have a subject ID of 2520-1001.

### 8.2. 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), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

## 9. SCHEDULE OF EVENTS

| **ASSESSMENTS** | **Screening** | **Treatment** | | | | | | | | | | | | | | **ONLY If EOT = Day 14[2,4]** | **ONLY If EOT = Day 14[2,4]** | **Continued Treatment visits for eligible subjects (CTV)** | **Follow-up** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Up to 72 hrs prior to Day 1 | Day 1 (baseline) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14[4] | Day 21 (+/- 2 days) | Day 28 (+/- 4 days) | Dosing Q 3 wks +/- 2 days: Week 5, 8, 11 | Week 12 for all subjects | 4 weeks (+/- 7 Days) after last Pamrevlumab dose |
| Informed consent | X | | | | | | | | | | | | | | | | | | | |
| Eligibility criteria | X | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | |
| Demographic information | X | | | | | | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | | | | | | | |
| Vital signs[3] | X | X[1] | X | X | X | X | X | X[1] | X | X | X | X | X | X | X[1] | | | X[1] | | |
| ECG | X | | | | | | | | | | | | | | | | | | | |
| Chest HRCT | X | | | | | | | | | | | | | | X | | | | X | |
| Laboratory assessments (local ) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | | |
| Blood samples for Immunogenicity Assessments | | X | | | | | | X | | | | | | | X | | | | | X |
| Urine pregnancy test[6] | X | | | | | | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Infusion | | X | | | | | | X | | | | | | | X | | | | | |
| Arterial Blood Gases (ABG)[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| $PaO_2/FiO_2$[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| Resting $SpO_2$ (3 times/day)[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| Oxygen supplementation Needs[3, 5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Survival and Hospital Discharge Status | | | | | | | | | | | | | | | | X | X | | X | X |

[1]On infusion days, vitals taken within 30 minutes prior and 30 min after infusion; otherwise vitals taken daily [2]Follow-up visits to be done in person or by phone [3]Only measured until subject is discharged from the ICU/CCU. [4]Subjects ending treatment on Day 14 should be contact by phone or return for a visit on Days 21 and 28 for a vital status check. [5]Including need for mechanical ventilation including ventilator settings, or supplemental oxygen including mode of oxygen delivery [6]Only for women of childbearing potential or last menstruation <1 year.