Protocol for

Official Title of Study

# A PHASE 2, 24-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY, WITH AN 80-WEEK ACTIVE TREATMENT EXTENSION, TO EVALUATE THE EFFICACY AND SAFETY OF CC-90001 IN SUBJECTS WITH IDIOPATHIC PULMONARY FIBROSIS

NCT03142191

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# A PHASE 2, 24-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY, WITH AN 80-WEEK ACTIVE TREATMENT EXTENSION, TO EVALUATE THE EFFICACY AND SAFETY OF CC-90001 IN SUBJECTS WITH IDIOPATHIC PULMONARY FIBROSIS

| | |
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| |
|---|
| *{See appended electronic signature page}* |
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| [redacted] |
| **Printed Name of Celgene Therapeutic Area Head and Title** |
| By my signature, I indicate I have reviewed this protocol and find its content to be acceptable. |

## SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
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| **Printed Name of Site Principal Investigator**<br><br>**Institution Name:** _____<br><br>By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies. | |

## COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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|---|---|
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# PROTOCOL SUMMARY

**Study Title**

A Phase 2, 24-Week, Randomized, Double-blind, Placebo-controlled, Multicenter Study, With an 80-Week Active Treatment Extension, to Evaluate the Efficacy and Safety of CC-90001 in Subjects With Idiopathic Pulmonary Fibrosis

**Indication**

Idiopathic Pulmonary Fibrosis (IPF)

**Objectives**

| **Primary Objective** |
|---|
| To evaluate the effect of CC-90001, 200 mg and 400 mg, when orally administered (PO) once daily (QD), compared with placebo, on percent of predicted forced vital capacity (FVC) after 24 weeks of treatment in subjects with IPF. |
| **Secondary Objective(s)** |
| To evaluate the effects of CC-90001, 200 mg and 400 mg PO QD, compared to placebo, after 24 weeks of treatment in subjects with IPF, on:<br>• FVC (milliliters [mL])<br>• Six-minute Walk Test (6MWT)<br>• Disease progression<br>• Health-related quality of life: St. George's Respiratory Questionnaire (SGRQ) and University of California San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)<br>• Dose response<br>• Safety and tolerability<br>To examine the effect of CC-90001 PO QD, compared to placebo, in subjects with progressive pulmonary fibrosis (PPF), on:<br>• Safety and tolerability |

[redacted]

**Study Design**

This is a Phase 2, multicenter, multinational, double-blind, randomized, placebo-controlled study evaluating the efficacy, safety, [redacted] quality of life [redacted] of two oral (PO) treatment doses of CC-90001 (200 mg and 400 mg QD), compared with placebo, for an initial 24 weeks of treatment, in subjects with IPF. This study will also assess the efficacy and long-term safety in the 80-week Active Treatment Extension Phase when all IPF subjects will receive CC-90001 (200 mg or 400 mg PO QD). This study is designed to assess response to treatment by using measures of lung function, disease progression, fibrosis on radiography, and patient-reported outcomes, including cough, dyspnea, and quality of life assessments. It will also assess dose response.

Approximately 165 adult male and female subjects with a diagnosis of IPF (Lynch, 2018) will be randomized 1:1:1 (55 subjects per arm) to treatment with CC-90001 (200 mg or 400 mg PO QD) or matching placebo for an initial 24 weeks. Subjects receiving concurrent protocol-allowable standard of care (SOC) therapy are eligible to participate in the study. Approximately 75 subjects (25 subjects per arm) receiving protocol-allowable SOC are to be enrolled in the study.

The randomization will be stratified based on the concurrent administration of protocol-allowable SOC (Yes/No). Subjects not receiving concurrent protocol-allowable SOC therapy will also be stratified by previous exposure to either pirfenidone or nintedanib (Yes/No).

[redacted]

Subjects completing 24 weeks of treatment will continue onto the 80-week Active Treatment Extension Phase.

Following an initial screening at Visit 1, eligible IPF subjects will be randomized to receive either CC-90001 200 mg or 400 mg PO QD or matching placebo beginning on Day 1 (Baseline [Visit 2]) of the study. At Week 24, all subjects originally randomized to receive placebo will be re-randomized 1:1 to blinded CC-90001 (200 mg or 400 mg PO QD) via interactive web response system (IWRS). All IPF subjects originally randomized to CC-90001 (200 mg or 400 mg PO QD) will remain on that same blinded treatment assignment during the 80-week Active Treatment Extension Phase. During the 80-week Active Treatment Extension Phase, all subjects not receiving concurrent protocol-allowable SOC therapy will have the opportunity, if deemed appropriate by the Investigator, to receive allowed SOC [redacted].

An interim analysis will be conducted when approximately 50 non-SOC IPF subjects have completed 24 weeks of treatment. If the safety and efficacy of CC-90001 are favorable, a separate exploratory substudy in subjects with progressive pulmonary fibrosis (PPF) will be initiated. The PPF substudy will enroll non-SOC subjects who do not receive a confirmed IPF diagnosis following central reading of high resolution computed tomography (HRCT) and lung biopsy (if obtained).

The exploratory substudy is a Phase 2, multicenter, multinational, double-blind, randomized, placebo-controlled study evaluating the efficacy, safety, [redacted] of one PO treatment dose regimen of CC-90001 (400 mg QD, unless review of benefit-risk favors 200 mg PO QD), compared with placebo, for an initial 24 weeks of treatment, in subjects with PPF. This substudy will also assess the efficacy and long-term safety in the 80-week Active Treatment Extension Phase when all PPF subjects will receive CC-90001. [redacted] Approximately 45 non-SOC subjects qualifying for enrollment into the substudy will be randomized in a 2:1 ratio to receive CC-90001 or matching placebo for an initial 24 weeks.

All subjects who complete the study treatment phases and those subjects who discontinue investigational product (IP) prior to the completion of the study will participate in the 4-week Post-treatment Observational Follow-up Phase.

To ensure the safety of all subjects in the study, the external Data Monitoring Committee (DMC) and Safety Management Team (SMT) will review safety data as described in the DMC charter and SMT plan. Close monitoring of safety data for all subjects will be conducted throughout the study and will include, but not be limited to, labs, electrocardiograms (ECGs), pulmonary function testing and adverse events.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

**Adjudication Committee**

This study will employ an independent adjudication committee that will adjudicate [redacted] hospitalizations and deaths. The adjudication committee will determine whether death(s) is associated with respiratory failure [redacted]. Details regarding the process and actions of this committee will be described in a separate charter.

**External Data Monitoring Committee**

Although the Celgene study staff will monitor safety on an ongoing basis throughout the study, formal unblinded safety and efficacy assessments of the study data will be performed by an independent external Data Monitoring Committee (DMC). The DMC is comprised of independent physician experts and a statistician who are not affiliated with the Sponsor and for whom there is no identified conflict of interest. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC charter.

The DMC will be also responsible for review of the interim analyses data and will make recommendations to a Celgene internal review committee (IRC), who will be responsible for final decision-making. The Celgene IRC members will not play a role in the study conduct and the blind will be maintained for persons responsible for the ongoing conduct and management of the study.

**Celgene Safety Management Team**

In addition to safety monitoring conducted by Investigators, site study personnel, and the Celgene study team, blinded study safety data will be reviewed by the Celgene SMT. The SMT is comprised of lead representatives from multiple Celgene functions engaged in the CC-90001 development program.

**Study Population**

The study population includes adult male and female subjects, ≥ 40 years of age with a confirmed diagnosis of IPF (Lynch, 2018), percent predicted forced vital capacity (FVC) ≥ 45% to ≤ 95%, and hemoglobin-corrected diffusion capacity of the lung for carbon monoxide ($D_LCO$) ≥ 25% to ≤ 90% predicted at Screening.

**Length of Study**

The study will have a total duration of up to 116 weeks. The study will consist of an up to 8-week Screening Phase; a 24-week Double-blind Placebo-controlled Treatment Phase; an 80-week Active Treatment Extension Phase; and a 4-week Post-treatment Observational Follow-up Phase.

The End of Trial is defined as either the date of the last visit of the last subject to complete the 4-week Post-treatment Observational Follow-up Phase or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as prespecified in the protocol (whichever is the later date).

**Study Treatments**

The IPF study subjects are provided with the following IP treatments:

- 24-Week Double-blind Placebo-controlled Treatment Phase: Baseline (Visit 2) to Week 24
  - CC-90001 400 mg PO QD
  - CC-90001 200 mg PO QD
  - Placebo PO QD
- 80-Week Active Treatment Extension Phase: Week 24 + 1 day to Week 104
  - CC-90001 400 mg PO QD
  - CC-90001 200 mg PO QD

The PPF substudy subjects are provided with the following IP treatments:

- 24-Week Double-blind Placebo-controlled Treatment Phase: Baseline (Visit 2) to Week 24
  - CC-90001 (400 mg PO QD, unless review of benefit-risk favors 200 mg PO QD)
  - Placebo PO QD
- 80-Week Active Treatment Extension Phase: Week 24 + 1 day to Week 104
  - CC-90001 (400 mg PO QD, unless review of benefit-risk favors 200 mg PO QD)

**Overview of Key Efficacy Assessments**

- Pulmonary Function Tests
  - FVC
  - $D_LCO$
  - Arterial oxygen saturation by pulse oximetry ($SpO_2$)
  - [redacted]
  - 6-minute Walk Test (6MWT) including Borg Scale Assessment

[redacted]

- Disease Progression

[redacted]

- Patient-reported Outcomes
  - St. George's Respiratory Questionnaire (SGRQ)

- University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ)

[redacted]

**Overview of Key Safety Assessments**

- Adverse events
- Physical examination, vital signs, and weight
- Clinical laboratory tests including hematology, chemistry, and urinalysis (including urine cytology)
- 12-lead electrocardiogram
- Pregnancy testing and pregnancy education

[redacted]

**Statistical Methods**

The primary objective of the study is to estimate the effect of CC-90001 in subjects with IPF either not receiving SOC or currently receiving SOC.

Approximately 165 subjects (55 subjects for CC-90001 200 mg with or without [±] SOC, 55 subjects for CC-90001 400 mg ± SOC, and 55 subjects for placebo ± SOC) provide 75% power for testing an overall difference of 2.2 percentage points or more in the Week 24 mean change from Baseline of percent predicted FVC value between either active treatment group ± SOC and the placebo group ± SOC (two-sided t-test; $\alpha = 0.1$; standard deviation [SD] = 5%), assuming that approximately 45% of subjects will be receiving concurrent protocol-allowable SOC based on the projected enrollment. The group size estimate is based on an assumed treatment difference of 3 in percent predicted FVC in the non-SOC cohort and 1.3 in percent predicted FVC in the SOC cohort at Week 24 from Baseline. The study will also estimate the effect of CC-90001 in the PPF cohort.

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# 1. INTRODUCTION

## 1.1. Disease Background

### 1.1.1. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and often lethal fibrosing interstitial lung disease of unknown etiology characterized by a poor prognosis (Raghu, 2011).

The reported prevalence of IPF varies geographically; for example, the published prevalence of IPF per 100,000 people ranges from 13-63 in the United States of America (USA) and from 3-23 in Europe (Ley, 2013). Approximately half of IPF patients either die or undergo lung transplantation within 3 to 5 years of diagnosis (Ley, 2013). The disease typically occurs in people between the ages of 40 and 70 years (median age is 66 years) and affects men more frequently than women. Most patients are former smokers. There are no proven risk factors for IPF, but < 5% of patients have a family history of interstitial lung disease (Raghu, 2011).

The diagnosis of IPF is made after excluding other conditions associated with pulmonary fibrosis and is based on a characteristic clinical presentation, radiographic features, and sometimes pathologic specimens (Raghu, 2011). The diagnosis of IPF requires information from several sources to be interpreted and integrated, and this can pose significant challenges in patient selection for this trial. Since the publication of the 2011 ATS/ERS guidelines (Raghu, 2011), diagnosing IPF continues to evolve through ongoing research and clinical experience. Very recently, a Fleischner Society White paper on the diagnostic criteria of IPF was published (Lynch, 2018). In this paper, a new category in the interpretation of high resolution computed tomography (HRCT) patterns, "computed tomography (CT) pattern indeterminate for usual interstitial pneumonia (UIP)," was proposed to encompass an HRCT that may be consistent with IPF and that lacks features most consistent with a non-IPF diagnosis. This new category can be considered a refinement of the 2011 ATS/ERS criteria, in which an HRCT classified as "inconsistent with UIP" did not distinguish between patients whose scans were insufficient to secure this diagnosis in the absence of additional information (eg, lung biopsy), from patients who were unlikely to have IPF.

IPF is characterized by interstitial fibrosis, which typically results in chronic irreversible scarring. These pathological changes are associated with a progressive decline in pulmonary function, which may lead to respiratory failure and death; some patients may experience episodes of acute respiratory worsening despite previous stability (Raghu, 2011).

The precise biological basis of IPF remains unclear. Over a lifetime, the lungs are exposed to repetitive injury from a variety of exogenous and endogenous stimuli. Several local and systemic factors (eg, fibroblasts, circulating fibrocytes, chemokines, growth factors, and clotting factors) contribute to tissue healing and functional recovery. Dysregulation of this intricate network, through genetic predisposition, autoimmune conditions, or superimposed diseases are proposed to lead to aberrant wound healing that may culminate in pulmonary fibrosis. Alternatively, excessive injury to the lung may overwhelm reparative mechanisms and may lead to pulmonary fibrosis (Nicholson, 2002; King, 2001).

In the recent past, the pharmacological treatment of IPF has changed considerably. Two approved treatments, pirfenidone and nintedanib, both appear to have modest effects on

progression-free survival and decline in pulmonary function (Noble, 2011; King, 2014; Richeldi, 2014). To date, lung transplantation has been shown to improve mortality in carefully selected patients (Kistler, 2014). Despite these advances, there remains a large unmet need for a safe and effective therapy for IPF that delays disease progression, improves pulmonary function, and reduces the mortality rate.

### 1.1.2. Progressive Forms of Pulmonary Fibrosis Other Than IPF

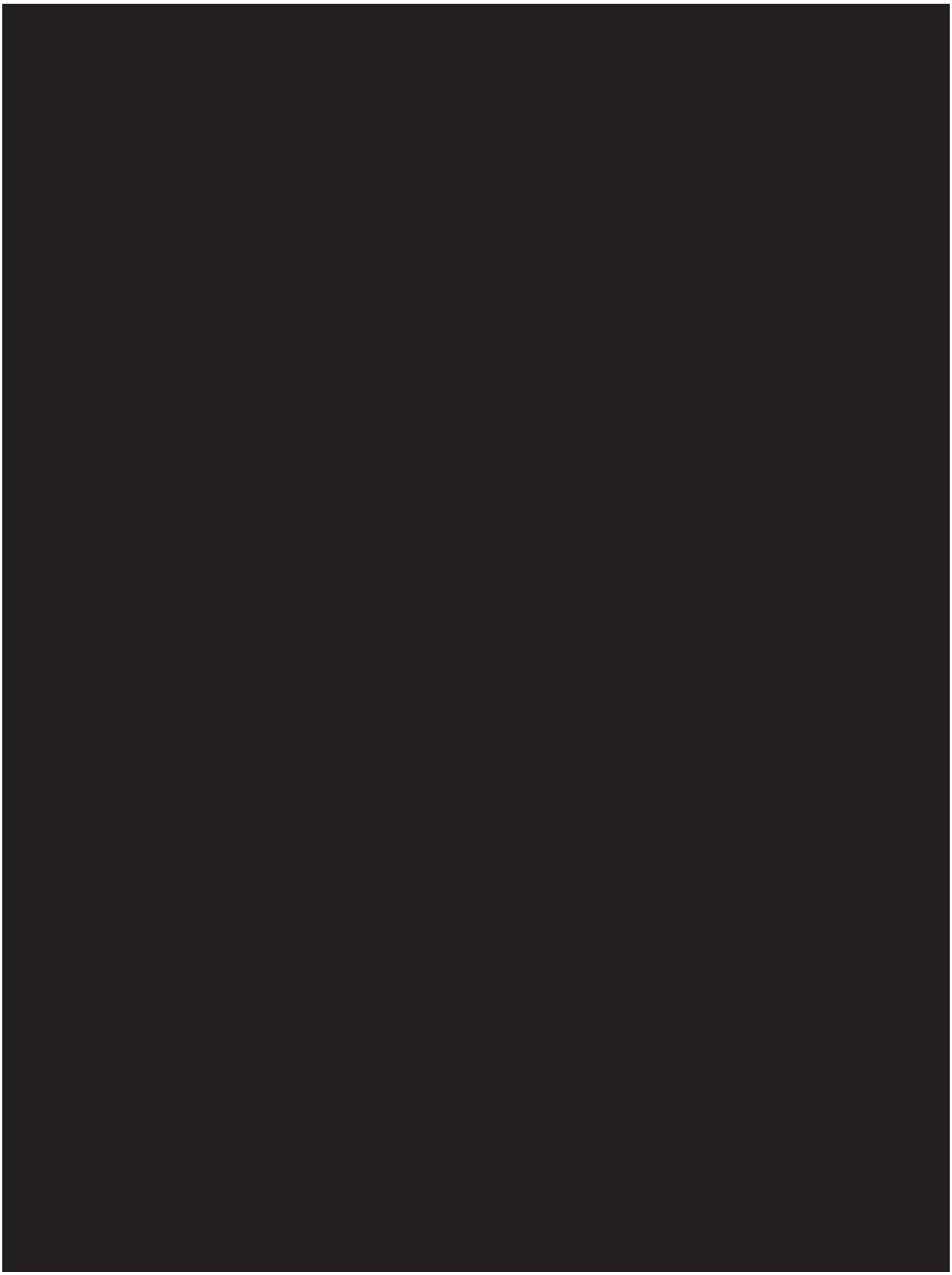
Besides IPF, other interstitial lung diseases (ILDs) can manifest as a progressive fibrosing phenotype (Wells, 2018; Cottin, 2018). The chest HRCT appearance in such individuals is variable and may conform to a UIP pattern similar to that in patients with IPF but can also be distinctive and be described as "indeterminate" for UIP or most consistent with a non-IPF diagnosis. Such cases would represent a radiological subset of "progressive-fibrosing ILD," a recently described term that recognizes the progressive nature of such ILDs (Flaherty, 2017; Cottin, 2018). Progressive fibrosis of the lung parenchyma causes progressive deterioration in lung function, respiratory symptoms and quality of life and therefore increases the risk of early death (Olson, 2016; Cottin, 2018).

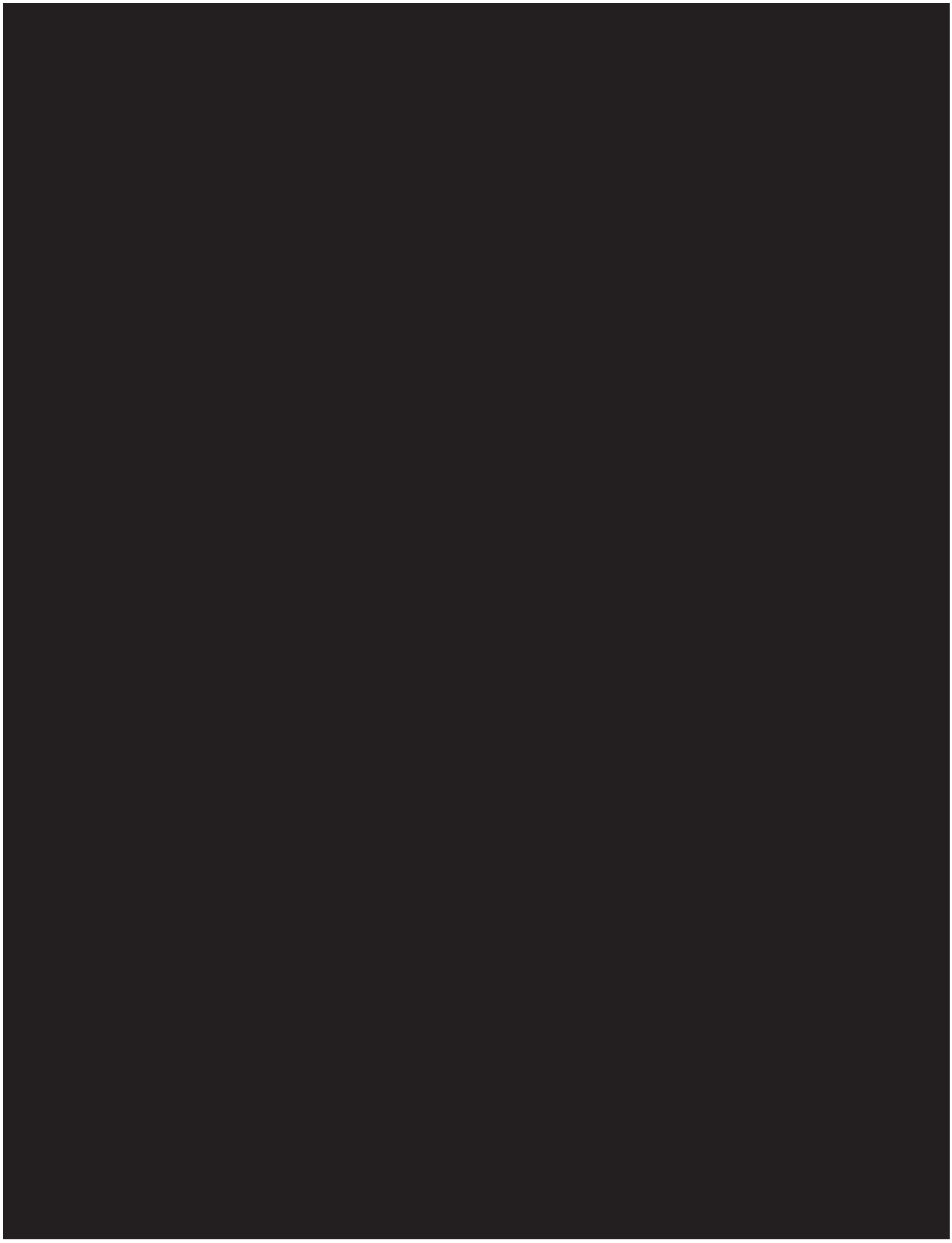
## 1.2. Compound Background

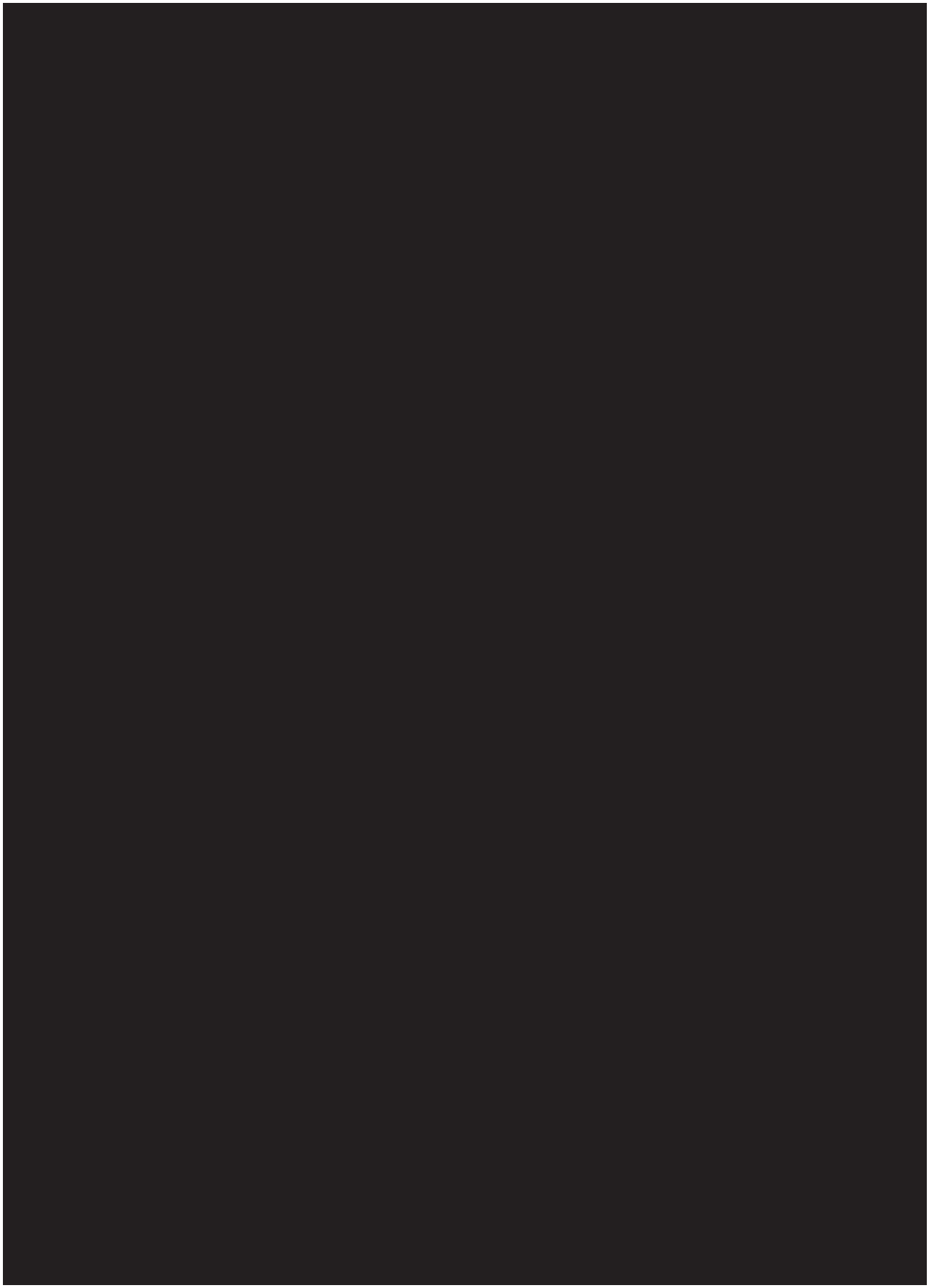
[redacted]

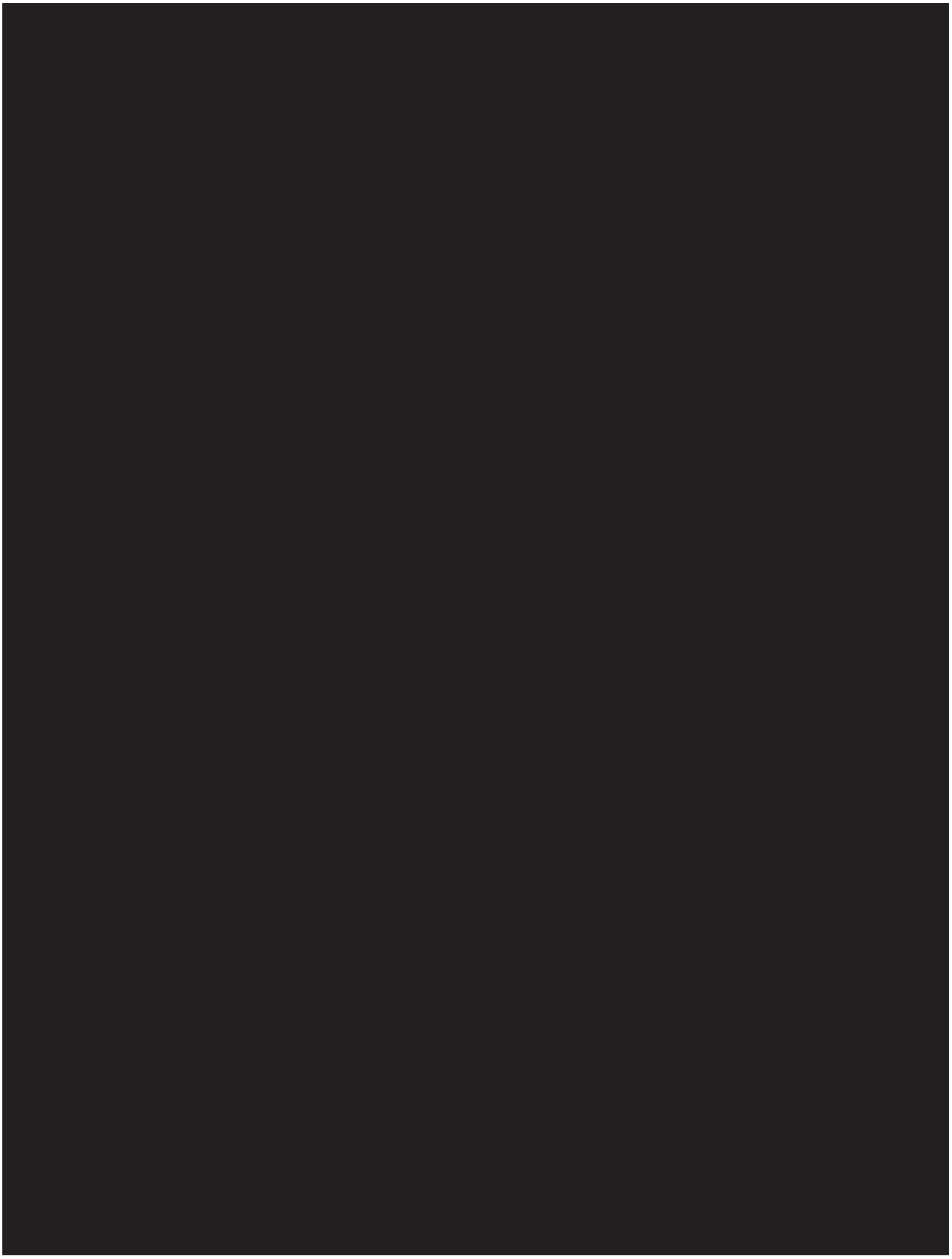
[redacted] CC-90001 is a potent inhibitor of JN [redacted]

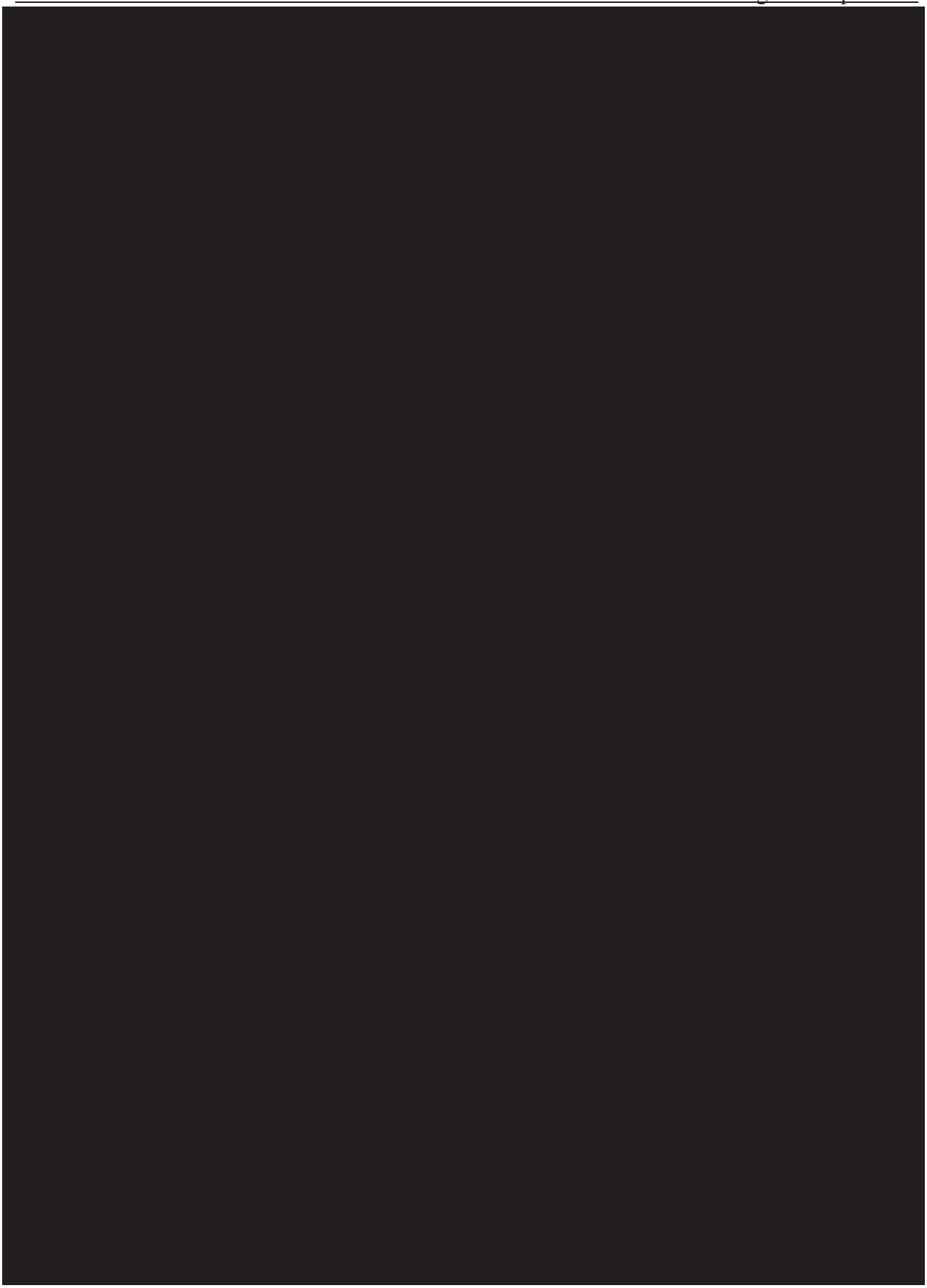
[redacted]

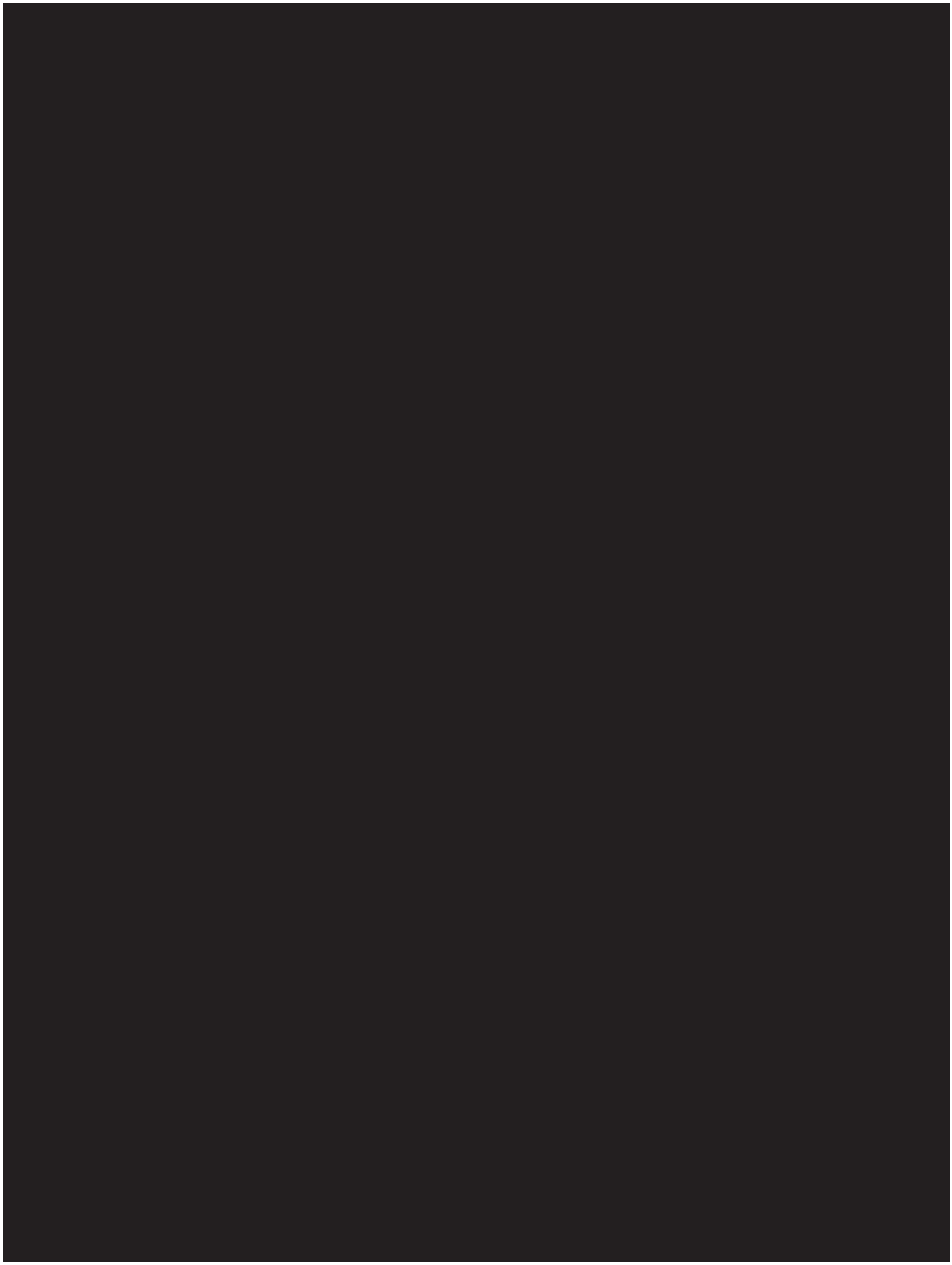












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## 1.6. Rationale

### 1.6.1. Study Rationale and Purpose

Most treatment strategies for fibrotic disorders like IPF have been based on eliminating or suppressing the inflammatory factors involved in the disease with immunosuppressive drugs, such as corticosteroids and cytotoxic agents. Although these drugs may reduce the inflammatory cascade by blocking the proliferation of cells and the recruitment of inflammatory leukocytes, or by killing recruited cells, these drugs do not necessarily target the underlying fibrotic response well, which typically involves both local cells (stromal cells) and recruited cells (inflammatory leukocytes) (Wynn, 2004). By inhibiting JNK, CC-90001 is hypothesized to interrupt both areas of this process. More recently, two pharmacological therapies, pirfenidone and nintedanib, commercially available in some regions of the world, have demonstrated modest effects on progression-free survival and decline in pulmonary function in patients with IPF (Noble, 2011; King, 2014; Richeldi, 2014). The relatively modest benefits associated with these agents for a disease as serious as IPF indicate that there remains an important, unmet need in the treatment of IPF. Based on recent insights into the pathogenesis of IPF, the underlying rationale for the current protocol is that JNK plays a pivotal role in the progression of pulmonary fibrosis and that inhibition of JNK, by CC-90001, will lead to improved lung function and other outcomes in patients with IPF.

### 1.6.2. Rationale for the Study Design

The Phase 3 pirfenidone and nintedanib trials demonstrated benefits on FVC in patients receiving active treatment, compared with placebo, after 52 weeks (King, 2014; Richeldi, 2014) and 72 weeks (Noble, 2011) of treatment, respectively. Apparent benefits in FVC were observed as early as 24 weeks following onset of treatment (Noble, 2011; King, 2014; Richeldi, 2014). Therefore, it is anticipated that a treatment response with CC-90001 in IPF should occur as early as 24 weeks after initiation of treatment, especially if the effect is robust. The 24-week Double-blind Placebo-controlled Treatment Phase should provide the shortest study duration to reasonably assess the efficacy and safety of CC-90001 with or without (±) standard of care (SOC) in IPF subjects. The 80-week Active Treatment Extension Phase will provide additional [redacted] long-term safety and efficacy information for CC-90001 ± SOC. It will also provide those subjects randomized to the placebo treatment without SOC the opportunity to receive active CC-90001 (200 mg or 400 mg PO QD).

### 1.6.3. Rationale for Selecting FVC as the Primary Endpoint

Change in FVC was selected as the primary endpoint because of its widespread clinical use and the clinical relevance of irreversible loss of lung function. Change in FVC is currently accepted by health authorities as a primary endpoint in IPF trials in part because it is a reliable, responsive

measurement. Deterioration in FVC ≥ 10% from baseline over 6 months has been shown to predict mortality in IPF patients (du Bois, 2011).

### 1.6.4. Rationale for Dose, Schedule and Regimen Selection

The 200 mg and 400 mg QD doses of CC-90001 were selected based on preclinical and clinical data in addition to simulation that supports adequate target engagement at clinically tolerated doses with sufficient PK distribution between doses. Additionally, exposures in this dose range are consistent with exposures required for efficacy in preclinical models.

[redacted]

#### 1.6.4.1. Biological Activity

[redacted] CC-930, a JNK inhibitor, was previously evaluated for activity in both UVB-induced phospho-c-Jun expression in healthy volunteers, and for safety in IPF subjects. In IPF subjects treated with CC-930, a dose-dependent trend in reducing plasma MMP-7 was observed, and changes in plasma MMP-7, SP-A, SP-D, and TNC levels significantly correlated with changes in FVC (Schafer, 2013; van der Velden, 2016). [redacted] Thus, the 200 and 400 mg doses

of CC-90001, which significantly inhibited the JNK pathway [redacted], phospho-c-Jun, are in a range that is expected to have an effect on the IPF [redacted].

### 1.6.5. Rationale for Placebo Comparator

A placebo control is needed in this Phase 2 trial to accurately determine the clinical benefits and safety profile of CC-90001.

The study embodies neither expectation nor intent that patients discontinue indicated and well-tolerated treatment to participate. Although both pirfenidone and nintedanib have demonstrated clinical benefits compared to placebo, these benefits have been modest and variable; many patients receiving these medications may fail to demonstrate clinically meaningful benefits and/or may experience significant tolerability issues or adverse reactions that limit their clinical utility. Clinical experience with CC-90001 thus far suggests that gastrointestinal-related AEs may occur in IPF, similar to those that occur following administration of pirfenidone and nintedanib. After Week 24 of this study, all subjects will be given the opportunity to receive CC-90001 (200 mg or 400 mg PO QD). In addition, if deemed appropriate by the Investigator, all subjects not receiving concurrent protocol-allowable SOC therapy will be permitted to receive allowed SOC [redacted].

[redacted]

[redacted]

### 1.6.7. Rationale for Patient-Reported Outcomes

In chronic, progressive and ultimately fatal diseases like IPF, assessment of health-related quality of life is especially useful in providing the patients' perspective on treatment benefit. These instruments are used to directly measure treatment benefit that is of greatest relevance to the patient. Patient-reported outcome instruments have been included in this study to document the effect of CC-90001 on symptoms and quality of life.

This study will implement three patient-reported outcomes, SGRQ, [redacted] and UCSD-SOBQ, to obtain preliminary information that will inform on which tools to use in the Phase 3 program. The SGRQ has been chosen as it has demonstrated acceptable psychometric characteristics in patients with IPF, including construct validity, reliability, and ability to detect change over time (Yorke, 2010; Swigris, 2010). [redacted] SGRQ

possess reasonable validity for differentiating subjects whose IPF disease severity changes over time (Swigris, 2010). The UCSD-SOBQ demonstrates content validity (Gries, 2013) and is able to detect changes in symptoms over time (Gries, 2013; Swigris, 2012) in patients with IPF (Swigris, 2012a).

## 1.7. Potential Risks of CC-90001 and the Study Population

Based on the Phase 1 studies in healthy subjects and the Phase 1b study in pulmonary fibrosis subjects, the TEAEs associated with administration of CC-90001 are mostly gastrointestinal in nature. Gastrointestinal TEAEs reported in these studies included nausea, diarrhea, indigestion, abdominal discomfort/cramping, emesis, and constipation. Headache, rash, dermatitis, fatigue and musculoskeletal pain TEAEs were also reported. The majority of the reported TEAEs were mild or moderate in severity. Some subjects who experienced nausea in the Phase 1 studies have reported less nausea when the IP was taken with food. There were no SAEs reported in the Phase 1 studies.

The Sponsor has instituted extensive safety monitoring into this protocol based upon potential risks associated with CC-90001 and the disease under study.

- Frequent study visits to assess safety laboratory results, including, but not limited to, liver function, white blood cell (WBC) count, hemoglobin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, pulmonary function and arterial oxygen saturation ($SpO_2$).
- Individual subject dose stopping rules and study stopping rules to ensure subjects are discontinued from CC-90001 in the event of severe liver toxicity. In a study conducted with the structurally unrelated pan-JNK inhibitor, CC-930, IPF subjects treated with high doses of CC-930 demonstrated abnormal liver function tests after approximately 8-12 weeks of daily dosing. In order to support this Phase 2 study with chronic dosing, the CC-90001-CP-003 study in pulmonary fibrosis subjects was conducted to understand the safety profile after a 12-week treatment duration.
- CC-90001 may be an inhibitor of liver transporters (eg, OATP1B1 and OATP1B3) and breast cancer resistance protein (BCRP). Therefore, subjects taking statins

concomitantly with CC-90001 may experience increased plasma concentrations of statins with prescribed doses. To ensure the safety of the subjects, concomitant statins will be dose adjusted to a therapeutic level (see Section 8.2.1).

- Urine cytology to examine for abnormal cellular findings.
- Electrocardiograms (ECGs) with centralized over-read and blood pressure measurements will be performed to monitor for potential cardiovascular effects.
- Required and frequent Investigator/Celgene safety review meetings to ensure appropriate and timely intervention (such as study discontinuation) in the event that a safety signal is identified.

Celgene is confident that the safety monitoring plan included within this protocol is sufficient to monitor for potential safety risks of CC-90001. In addition, provisions for monitoring for disease-specific complications, such as hypoxemia and decline in pulmonary function secondary to disease progression, have also been included as part of the protocol design.

# 2. STUDY OBJECTIVES AND ENDPOINTS

**Table 1: Study Objectives**

| **Primary Objective** |
|---|
| To evaluate the effect of CC-90001, 200 mg and 400 mg, when orally administered (PO) once daily (QD), compared with placebo, on percent of predicted forced vital capacity (FVC) after 24 weeks of treatment in subjects with idiopathic pulmonary fibrosis (IPF). |
| **Secondary Objectives** |
| To evaluate the effects of CC-90001, 200 mg and 400 mg PO QD, compared to placebo, after 24 weeks of treatment in subjects with IPF, on:<br>• FVC (milliliters [mL])<br>• Six-minute Walk Test (6MWT)<br>• Disease progression<br>• Health-related quality of life: St. George's Respiratory Questionnaire (SGRQ) and University of California San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)<br>• Dose response<br>• Safety and tolerability<br>To examine the effect of CC-90001 PO QD, compared to placebo, in subjects with progressive pulmonary fibrosis (PPF), on:<br>• Safety and tolerability |

**Table 1: Study Objectives (Continued)**

**Table 1: Study Objectives (Continued)**

**Table 2: Idiopathic Pulmonary Fibrosis Study Endpoints**

| Endpoint | Name | Description | Timeframe |
|---|---|---|---|
| Primary | Forced vital capacity (FVC) | Percentage point difference in % predicted FVC | Baseline to Week 24 |
| Secondary | FVC | Absolute change and rate of decline in FVC (expressed in mL) | Baseline through Week 24 |
| Secondary | 6-minute Walk Test (6MWT) with Borg Scale | Change in the distance walked during the 6MWT as measured in meters (m)<br>Change in dyspnea rating on Borg Scale | Baseline to Week 24;<br>Baseline to Week 52;<br>Baseline to Week 76;<br>Baseline to Week 104;<br>Week 24 to Week 52;<br>Week 24 to Week 104 |
| Secondary | Disease progression | Disease progression is defined as one or more of the following:<br>• Death from respiratory failure, or<br>• Absolute decrease of ≥ 10% from baseline in % predicted FVC at two consecutive evaluations at a minimum of 4 weeks between evaluations, or<br>• Decrease from baseline of ≥ 50 meters in 6MWT distance (in the absence of a readily explainable cause, such as injury or trauma), or<br>• Unexplained worsening hypoxemia (an absolute decrease from baseline of 4% or more in arterial oxygen saturation by pulse oximetry [$SpO_2$]). | Baseline through Week 24 |
| Secondary | Quality of life | Change from Baseline in total score and domains on the Saint George's Respiratory Questionnaire (SGRQ) | Baseline through Week 24 |
| | | Change from Baseline in the University of California San Diego Shortness of Breath Questionnaire (UCSD- SOBQ) | Baseline through Week 24 |

**Table 2: Idiopathic Pulmonary Fibrosis Study Endpoints (Continued)**

| Endpoint | Name | Description | Timeframe |
|---|---|---|---|
| Secondary | Safety and tolerability | Type, frequency, severity, and relationship of adverse events (AEs), clinical laboratory tests including urine cytology, 12-lead electrocardiogram (ECG), vital signs, and physical examination | Signing of the informed consent form through Week 108 (4-week post-treatment observational follow-up) |
| [redacted] | | | |

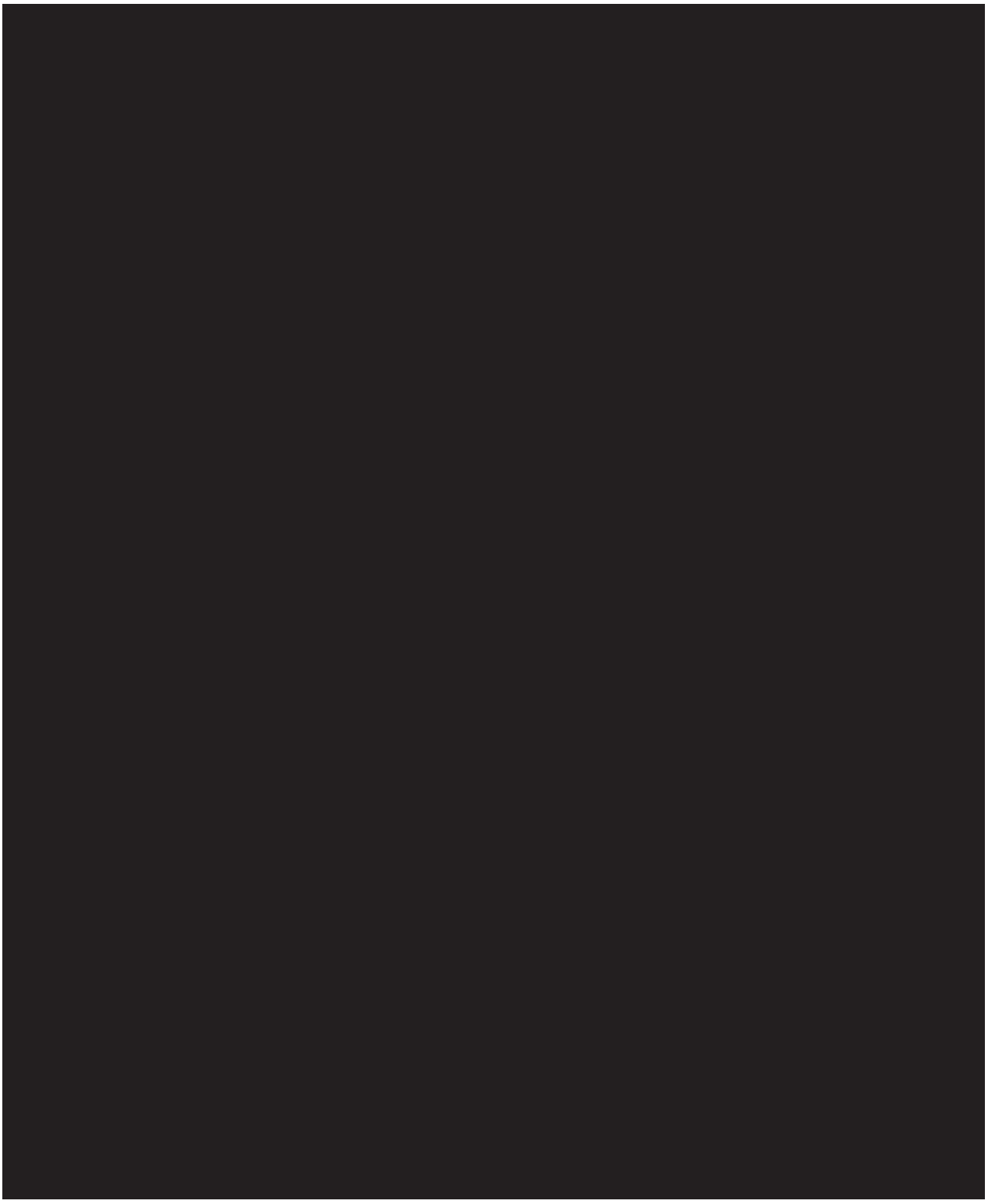
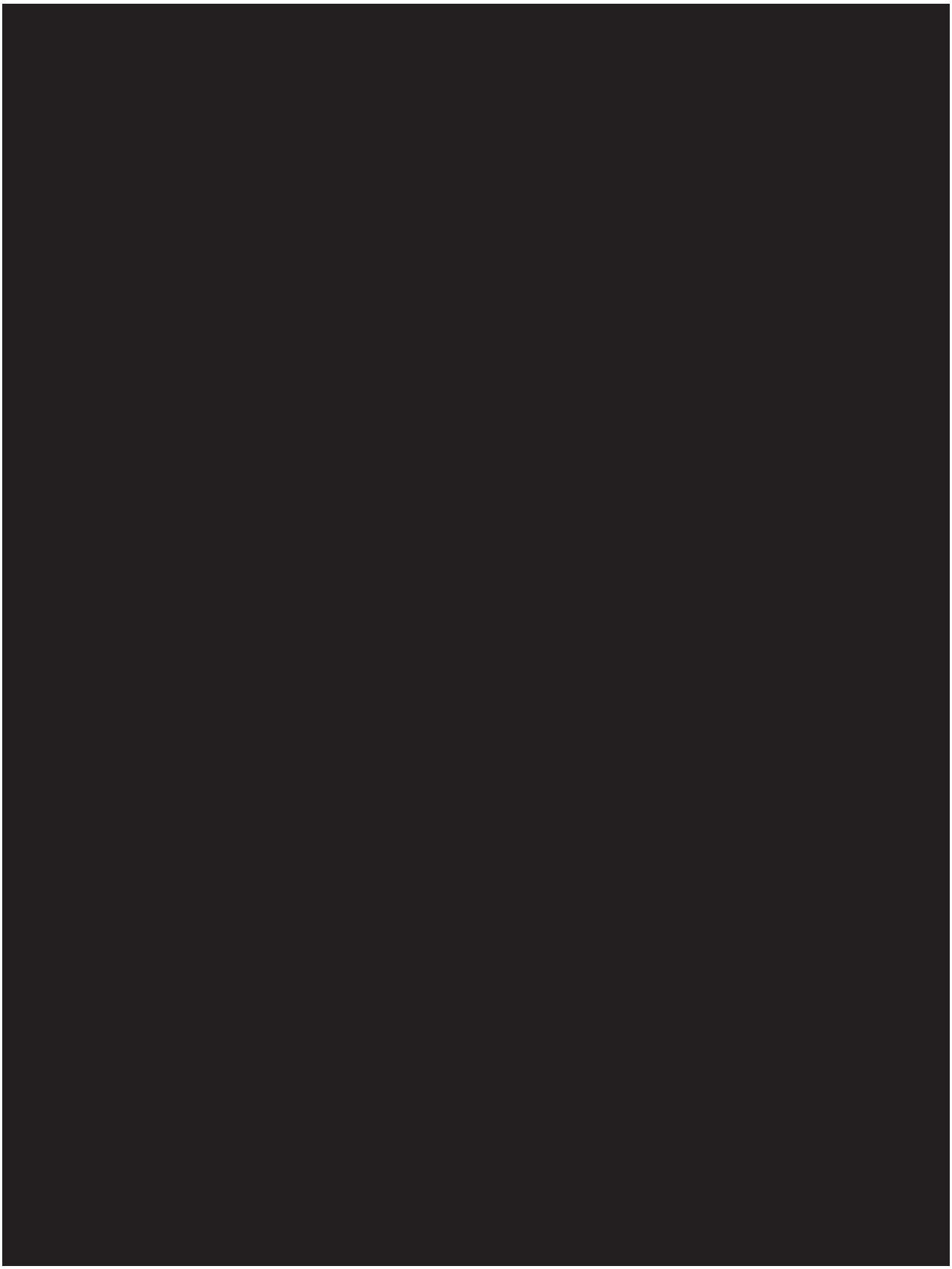


**Table 3: Progressive Pulmonary Fibrosis Substudy Endpoints**

| Endpoint | Name | Description | Timeframe |
|---|---|---|---|
| Secondary | Safety and tolerability | Type, frequency, severity, and relationship of adverse events (AEs), clinical laboratory tests including urine cytology, 12-lead electrocardiogram (ECG), vital signs, and physical examination | Signing of the informed consent form through Week 108 (4-week post-treatment observational follow-up) |
| [redacted] | | | |



# 3. OVERALL STUDY DESIGN

## 3.1. Study Design

This is a Phase 2, multicenter, multinational, double-blind, randomized, placebo-controlled study evaluating the efficacy, safety, [redacted] quality of life [redacted] of two oral (PO) treatment doses of CC-90001 (200 mg and 400 mg QD), compared with placebo, for an initial 24 weeks of treatment, in subjects with IPF. This study will also assess the efficacy and long-term safety in the 80-week Active Treatment Extension Phase when all IPF subjects will receive CC-90001 (200 mg or 400 mg PO QD). This study is designed to assess response to treatment by using measures of lung function, disease progression, fibrosis on radiography, and patient-reported outcomes, including cough, dyspnea, and quality of life assessments. It will also assess dose response.

Approximately 165 adult male and female subjects with a diagnosis of IPF (Lynch, 2018) will be randomized 1:1:1 (55 subjects per arm) to treatment with CC-90001 (200 mg or 400 mg PO QD) or matching placebo for an initial 24 weeks. Subjects receiving concurrent protocol-allowable standard of care (SOC) therapy are eligible to participate in the study. Approximately 75 subjects (25 subjects per arm) receiving protocol-allowable SOC are to be enrolled in the study. The randomization will be stratified based on the concurrent administration of protocol-allowable SOC (Yes/No). Subjects not receiving concurrent protocol-allowable SOC therapy will also be stratified by previous exposure to either pirfenidone or nintedanib (Yes/No). [redacted] Subjects completing 24 weeks of treatment will continue onto the 80-week Active Treatment Extension Phase. Subjects who enter and complete the 80-week Active Treatment Extension Phase will receive treatment for a total of 104 weeks (Figure 1).

Following an initial screening at Visit 1, eligible IPF subjects will be randomized to receive either CC-90001 200 mg or 400 mg PO QD or matching placebo beginning on Day 1 (Baseline [Visit 2]) of the study. At Week 24, all subjects originally randomized to receive placebo will be re-randomized 1:1 to blinded CC-90001 (200 mg or 400 mg PO QD) via interactive web response system (IWRS). All IPF subjects originally randomized to CC-90001 (200 mg or 400 mg PO QD) will remain on that same blinded treatment assignment during the 80-week Active Treatment Extension Phase. During the 80-week Active Treatment Extension Phase, all subjects not on concurrent protocol-allowable SOC therapy will have the opportunity, if deemed appropriate by the Investigator, to receive allowed SOC [redacted].

An interim analysis will be conducted when approximately 50 non-SOC IPF subjects have completed 24 weeks of treatment. If the safety and efficacy of CC-90001 are favorable, a separate [redacted] substudy in subjects with progressive pulmonary fibrosis (PPF) will be initiated (refer to Section 3.1.1).

A second interim analysis is planned after approximately 40 SOC IPF subjects have completed 24 weeks of treatment. The purpose of the additional interim analysis is to evaluate safety, tolerability and efficacy of CC-90001 in SOC IPF subjects, along with all study subjects enrolled into the study, and to determine if any treatment group should be discontinued.

All subjects who complete the study treatment phases and those subjects who discontinue investigational product (IP) prior to the completion of the study will participate in the 4-week Post-treatment Observational Follow-up Phase.

To ensure the safety of all subjects in the study, the external Data Monitoring Committee (DMC) and SMT will review safety data as described in the DMC charter and SMT plan. Close monitoring of safety data for all subjects will be conducted throughout the study and will include, but not be limited to, labs, ECGs, pulmonary function testing, and adverse events.

The blind should be maintained for persons responsible for the ongoing conduct of the study from first subject enrolled through last subject/last visit of the 4-week Post-Treatment Follow-up Phase of the study. Blinded persons may include but are not limited to: Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, Clinical Research Associates.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

### 3.1.1. Progressive Pulmonary Fibrosis Substudy

The exploratory substudy is a Phase 2, multicenter, multinational, double-blind, randomized, placebo-controlled study evaluating the efficacy, safety, [redacted] of one PO treatment dose regimen of CC-90001 (400 mg QD, unless review of benefit-risk favors 200 mg PO QD), compared with placebo, for an initial 24 weeks of treatment, in subjects with PPF. This substudy will also assess the efficacy and long-term safety in the 80-week Active Treatment Extension Phase when all PPF subjects will receive CC-90001. [redacted] This PPF substudy allows non-SOC subjects who were screened and did not receive a confirmed IPF diagnosis following central reading of HRCT and lung biopsy, if obtained, to be considered for the substudy. Enrollment into this substudy will not begin until after the first interim analysis and confirmation is received from the DMC that the overall main study in IPF subjects should continue as planned (Section 9.8).

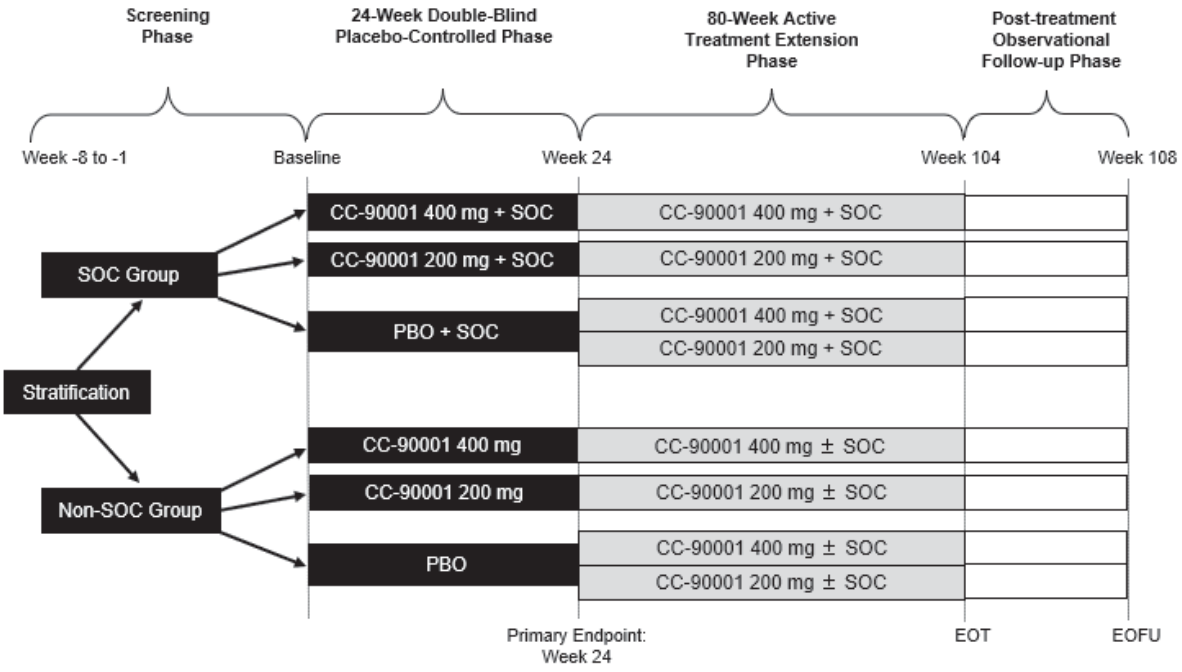
Approximately 45 non-SOC subjects qualifying for enrollment into the substudy will be randomized in a 2:1 ratio (approximately 30 subjects in the CC-90001 arm and approximately 15 subjects in the placebo arm), for an initial 24 weeks. Subjects who enter and complete the 80-week Active Treatment Extension Phase will receive treatment for a total of 104 weeks. Refer to Figure 2 for the PPF substudy design and Section 4.2.2 for specific inclusion criteria.

Following an initial screening at Visit 1, eligible PPF subjects will be randomized to receive either CC-90001 or matching placebo beginning on Day 1 (Baseline [Visit 2]) of the study. At Week 24, all subjects originally randomized to receive placebo will receive CC-90001. All subjects originally randomized to CC-90001 will remain on that same blinded treatment assignment during the 80-week Active Treatment Extension Phase. The decision to receive additional treatments for pulmonary fibrosis [redacted] during the 80-week Active Treatment Extension Phase is at the discretion of the Investigator.

### 3.1.2. Adjudication Committee

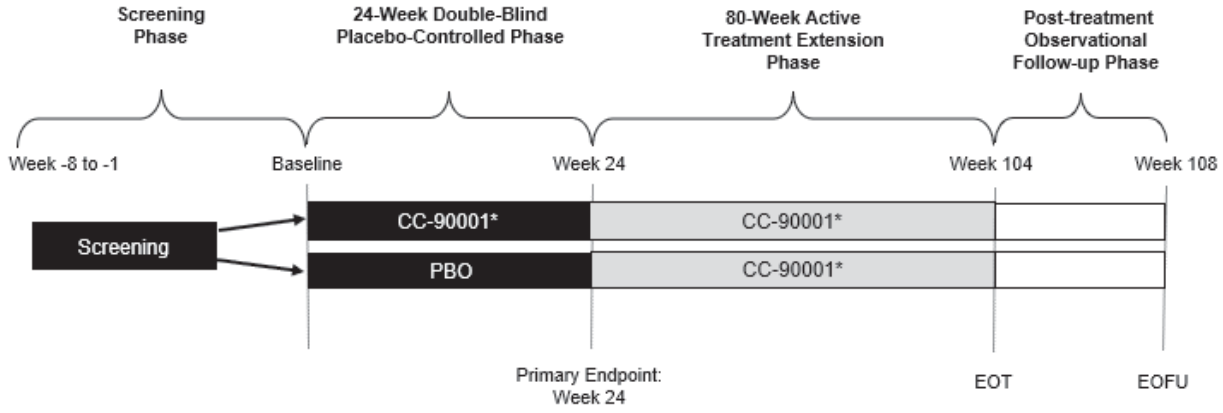
This study will employ an independent adjudication committee that will adjudicate [redacted] hospitalizations and deaths. The adjudication committee will determine whether death(s) is associated with respiratory failure [redacted]. Details regarding the process and actions of this committee will be described in a separate charter.

**Figure 1: Overall Study Design (Idiopathic Pulmonary Fibrosis Study)**




Abbreviations: EOFU = end of follow-up; EOT = end of treatment; PBO = placebo;
SOC = standard of care [redacted].

**Figure 2: Overall Study Design (Progressive Pulmonary Fibrosis Substudy)**




Abbreviations: EOFU = end of follow-up; EOT = end of treatment; PBO = placebo.
* CC-90001 400 mg orally (PO) once daily (QD) is the intended dose regimen, unless review of benefit-risk favors 200 mg PO QD.

## 3.2. Study Duration for Subjects

The study will have a total duration of up to 116 weeks. The study will consist of an up to 8-week Screening Phase; a 24-week Double-blind Placebo-controlled Treatment Phase; an 80-week Active Treatment Extension Phase; and a 4-week Post-treatment Observational Follow-up Phase.

## 3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as prespecified in the protocol, whichever is the later date.

# 4. STUDY POPULATION

## 4.1. Number of Subjects

Approximately 210 subjects will be randomized worldwide. Approximately 165 subjects diagnosed with IPF will be randomized into the study and approximately 45 additional subjects will be randomized into the PPF substudy.

## 4.2. Inclusion Criteria

### 4.2.1. Inclusion Criteria for Idiopathic Pulmonary Fibrosis Subjects

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is male or female ≥ 40 years of age at the time of signing the informed consent form (ICF)
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4. Investigator has considered all available IPF treatment options with the potential subject before consenting the subject for participation in the study
5. Diagnosis of IPF is supported by HRCT, as described in Table 4 and Appendix G.

*Note: Historical lung biopsy (surgical lung biopsy [SLB] or lung cryobiopsy) may be used for eligibility, if available. HRCT scan performed within 18 months of randomization may be used if it meets image acquisition guidelines and scan is reviewed by centralized review. For sites subject to regulatory restrictions that do not permit HRCT within this time period, a previous HRCT scan is permissible if the scan is deemed sufficient for centralized review.*

**Table 4: Summary of Criteria for Diagnosis of Idiopathic Pulmonary Fibrosis Based on High Resolution Computed Tomography and Lung Biopsy**

| UIP Pattern on HRCT[a] | Histopathological Criteria for UIP in IPF (UIP-IPF)[a] | | | | |
|---|---|---|---|---|---|
| | Lung Biopsy Not Available Or Non-Diagnostic | Definite UIP-IPF | Probable UIP-IPF | Indeterminate UIP-IPF | Features Most Consistent With An Alternative Diagnosis |
| **Typical** | Eligible | Eligible | Eligible | Eligible | Ineligible |
| **Probable, ≤ 60 years of age** | Ineligible | Eligible | Eligible | Ineligible | Ineligible |
| **Probable, > 60 years of age** | Eligible | Eligible | Eligible | Eligible | Ineligible |
| **Indeterminate** | Ineligible | Eligible | Eligible | Ineligible | Ineligible |
| **Most consistent with non-IPF diagnosis** | Ineligible | Ineligible | Ineligible | Ineligible | Ineligible |

Abbreviations: HRCT = high resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.
[a] Criteria are described in Appendix G; adapted from Lynch, 2018 and Chung, 2018.

6. Extent of fibrotic changes (eg, honeycombing, reticular changes) greater than the extent of emphysema on HRCT scan, as determined by centralized review
7. No features supporting an alternative diagnosis on transbronchial biopsy, bronchoalveolar lavage (BAL), or SLB, if performed prior to Screening
8. Percent predicted forced vital capacity (FVC) ≥ 45% and ≤ 95% at Screening confirmed by centralized review
9. Change in FVC (measured in milliliters [mL]) between Screening and Day 1 less than a 10% relative difference, calculated as: the absolute value of 100% * (Screening FVC [mL] - Day 1 FVC [mL]) / Screening FVC (mL)
10. Hemoglobin-corrected percent predicted diffusion capacity of the lung for carbon monoxide ($D_LCO$) ≥ 25% and ≤ 90% predicted at Screening
11. Able to walk ≥ 150 meters during the 6-minute walk test (6MWT) at Screening
12. Females of childbearing potential (FCBP) [1] must:
    a. Have two negative pregnancy tests as verified by the Investigator prior to starting IP. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.

[1] A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use two effective birth control methods (one of which is highly effective) at the same time, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 28 days after discontinuation of IP.

Approved options for birth control are:

- Any one of the following highly effective methods: Hormonal contraception (for example, birth control pills, intravaginal ring, transdermal patch, injection, implant); intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a vasectomy.

  *Note: Certain drugs may reduce the effectiveness of hormonal contraceptives during and up to one month after discontinuation of these concomitant therapies.*

- Any effective method, for example, condoms.

13. Male subjects must:

    Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a latex condom or nonlatex condom not made out of natural (animal) membrane (eg, polyurethane) during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following IP discontinuation, even if he has undergone a successful vasectomy.

14. For subjects stratified to the protocol-allowable standard of care therapy group (only):

    Subjects must be receiving and agree to maintain the same dose of protocol-allowable standard of care (SOC) therapy for at least 8 weeks prior to Screening Visit 1 and must agree to continue this dose through Visit 9/Week 24. [redacted]

### 4.2.2. Inclusion Criteria for Progressive Pulmonary Fibrosis Substudy Only

Progressive pulmonary fibrosis subjects must satisfy the following criteria to be enrolled in the substudy:

15. Met all inclusion criteria described for IPF subjects in Section 4.2.1 other than Inclusion Criterion 5 (ie, not received an "eligible" designation based on Table 4)
16. Features of diffuse fibrosing lung disease of > 10% on HRCT by central reading

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

17. Investigator-documented ≥ 5% annualized relative decline in FVC in past 24 months from Screening Visit 1 (Examples: ≥ 10% relative decline in past 2 years; ≥ 5% relative decline in past year; ≥ 2.5% relative decline in past 6 months)

## 4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
3. Subject has any condition that confounds the ability to interpret data from the study
4. Significant clinical worsening of pulmonary fibrosis between Screening and Baseline (Visit 2), in the opinion of the Investigator
5. Subjects with any of the following laboratory criteria:
   - White blood cell count (WBC) < 3500/$mm^3$ (< 3.5 X $10^9$/L) or > 14,000/$mm^3$ (> 14 X $10^9$/L)
   - Platelet count < 120,000/μL (< 120 X $10^9$/L)
   - Serum creatinine > 1.5 mg/dL (> 132.6 μmol/L)
   - Aspartate aminotransferase (AST/SGOT) > 1.5 X upper limit of normal (ULN)
   - Alanine aminotransferase (ALT/SGPT) > 1.5 X upper limit of normal (ULN)
   - Total bilirubin > 2 mg/dL (> 34.2 μmol/L)
   - Hemoglobin < 10 g/dL (< 100 g/L)
6. Subject with a QTcF > 450 msec
7. Any condition other than pulmonary fibrosis that in the opinion of the Investigator is likely to result in the death of the subject within the next year
8. Inability to obtain reproducible, high-quality pulmonary function tests.
9. Evidence of clinically relevant airways obstruction (ie, $FEV_1$/FVC < 0.7) at Screening and/or significant respiratory disorder/pathology (eg, pulmonary arterial hypertension requiring treatment, asthma, tuberculosis, sarcoidosis, hypersensitivity pneumonitis, aspergillosis, asbestosis, neoplastic disease, cystic fibrosis or other interstitial lung disease) other than IPF

   *Note: Following central readings of HRCTs and central reviews of lung biopsies, if performed, underlying causes of pulmonary fibrosis in subjects enrolled in the PPF substudy may include fibrotic lung diseases other than IPF.*
10. Subject is likely to have lung transplantation during the first 24 weeks of the study (being on transplantation list is acceptable for participation)

11. Impairment (other than dyspnea) limiting the ability to comply with study requirements (eg, pulmonary function tests, 6-minute walk test)
12. Subjects using the following medications: [redacted] endothelium receptor antagonists (eg, bosentan, ambrisentan), interferon gamma-1b, imatinib mesylate, N-acetylcysteine, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, cyclosporine, and oral steroids (eg, prednisone > 12.5 mg/day or equivalent) within 4 weeks prior to the Screening Visit.

    *Note: Subjects should not discontinue any of these therapies for the sole purpose of participating in this study.*
13. Use of any cytokine modulator/biologic, such as etanercept, adalimumab, efalizumab, infliximab, or rituximab within 12 weeks of randomization
14. Use of an inhaled long-acting bronchodilator within 24 hours of the Screening Visit or short-acting bronchodilator within 8 hours of the Screening Visit
15. Use of drugs that are known to cause hepatotoxicity, such as, but not limited to, acetaminophen (paracetamol) at dosages of > 3 grams/day and niacin dosage of > 2 grams/day while on study or within 2 weeks of first dose of IP
16. Use of any medications that are substrates of one or more of the transporters P-gp, BCRP, OAT3, OATP1B1, OATP1B3, and OCT2 and have a narrow therapeutic index (eg, digoxin, mycophenolate mofetil)
17. History of recent (within 6 months of Screening) deep vein thrombosis (DVT) or pulmonary embolism (PE) and/or recurrent DVT or recurrent PE
18. History of cardiac valve replacement requiring chronic anticoagulation therapy
19. History of congenital and/or acquired immunodeficiencies (eg, common variable immunodeficiency, human immunodeficiency virus [HIV], etc)
20. History of hepatitis B and/or hepatitis C, including those considered successfully treated/cured
21. Active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including, but not limited to, atypical mycobacterial disease and herpes zoster), or any major episode of infection requiring hospitalization or treatment with intravenous or oral antibiotics within 4 weeks of the Screening Visit and at any time during the Screening Phase, up through the first dose of IP
22. History of active or latent tuberculosis (TB) infection, unless there is medical record documentation of successful completion of a standard course of treatment considered appropriate, based on local prevalence of multi-drug resistant TB and consistent with World Health Organization guidelines

    *Note: If a subject has adequate documentation of successful treatment for either latent or active TB, the QuantiFERON-TB Gold test is not needed. Instead, a chest radiograph, obtained within the 12 weeks prior to Screening or during Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, will be*

*sufficient to permit further participation in the study for these subjects. Documentation of adequate treatment for TB must be obtained prior to randomization.*

23. Subject has had a household contact with a person with active TB and subject did not receive appropriate and documented prophylaxis for TB

    *Note: Household contact is a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment.*

24. Clinical diagnosis of any connective tissue disease, including, but not limited to, scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis
25. History of end-stage renal disease requiring dialysis
26. History of severe hepatic impairment or end-stage liver disease
27. History of Gilbert's syndrome
28. History of alcohol or drug abuse within 6 months prior to Screening
29. Use of tobacco products (cigarettes, pipes and cigars), vapes, e-cigarettes or marijuana use within 3 months of Screening and/or unwillingness to avoid the use of these products throughout the study
30. History of malignancy (exceptions: excised and cured basal/squamous cell skin carcinomas or cervical carcinoma in situ with no recurrence in 5 years)
31. Pregnancy or lactation
32. Use of any investigational drug within one month of Screening, or 5 PD/PK half-lives (whichever is longer)

# 5. TABLE OF EVENTS

**Table 5: Table of Events**

| | Screening Phase | 24-Week Double-Blind Placebo-Controlled Treatment Phase | | | 80-Week Active Treatment Extension Phase | | | | Early Termination Visit | Post-Treatment Observational Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit(s)[k]** | **1 Screening** | **2 Baseline[a]** | **3** | **4-9 Every 4 Weeks** | **10E** | **11E-17E Every 4 Weeks** | **18E-25E Every 6 Weeks** | **26E End of Treatment** | | **27E** |
| **Week(s)** | **-8 to -1** | **0** | **1 ± 3 days** | **4, 8, 12, 16, 20, 24 ± 3 days** | **25 ± 3 days** | **28, 32, 36, 40, 44, 48, 52 ± 3 days** | **58, 64, 70, 76, 82, 88, 94, 100 ± 3 days** | **104 ± 3 days** | | **108 4-weeks post-treatment ± 3 days** |
| Main Informed Consent | X | - | - | - | - | - | - | - | - | - |
| [redacted] | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | - | - | - | - | - | - | - | - |
| Demographics | X | - | - | - | - | - | - | - | - | - |
| Complete Medical History | X | - | - | - | - | - | - | - | - | - |
| Prior IPF Disease History | X | - | - | - | - | - | - | - | - | - |
| Prior IPF Therapies | X | - | - | - | - | - | - | - | - | - |

**Table 5: Table of Events (Continued)**

| | Screening Phase | 24-Week Double-Blind Placebo-Controlled Treatment Phase | | | 80-Week Active Treatment Extension Phase | | | | Early Termination Visit | Post-Treatment Observational Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit(s)[k]** | **1 Screening** | **2 Baseline[a]** | **3** | **4-9 Every 4 Weeks** | **10E** | **11E-17E Every 4 Weeks** | **18E-25E Every 6 Weeks** | **26E End of Treatment** | | **27E** |
| **Week(s)** | **-8 to -1** | **0** | **1 ± 3 days** | **4, 8, 12, 16, 20, 24 ± 3 days** | **25 ± 3 days** | **28, 32, 36, 40, 44, 48, 52 ± 3 days** | **58, 64, 70, 76, 82, 88, 94, 100 ± 3 days** | **104 ± 3 days** | | **108 4-weeks post-treatment ± 3 days** |
| Prior/ Concomitant Medication Evaluation | Continuous starting after the informed consent form is signed through 28 days after treatment | | | | | | | | | |
| Prior/Concomitant Procedures Evaluation | Continuous starting after the informed consent form is signed through 28 days after treatment. | | | | | | | | | |
| Postmenopausal testing: estradiol and follicle-stimulating hormone (for women without a menses for 1 year and/ or undocumented status) | X | - | - | - | - | - | - | - | - | - |
| QuantiFERON® -TB Gold Test or Chest Radiograph for TB when appropriate [l], Hepatitis B & C Tests | X | - | - | - | - | - | - | - | - | - |
| **SAFETY ASSESSMENTS** | | | | | | | | | | |
| Adverse Event Evaluation | Continuous starting after the informed consent form is signed through 28 days after treatment. | | | | | | | | | |





[redacted]

**Table 5: Table of Events (Continued)**

| | Screening Phase | 24-Week Double-Blind Placebo-Controlled Treatment Phase | | | 80-Week Active Treatment Extension Phase | | | | Early Termination Visit | Post-Treatment Observational Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit(s)[k]** | **1 Screening** | **2 Baseline[a]** | **3** | **4-9 Every 4 Weeks** | **10E** | **11E-17E Every 4 Weeks** | **18E-25E Every 6 Weeks** | **26E End of Treatment** | | **27E** |
| **Week(s)** | **-8 to -1** | **0** | **1 ± 3 days** | **4, 8, 12, 16, 20, 24 ± 3 days** | **25 ± 3 days** | **28, 32, 36, 40, 44, 48, 52 ± 3 days** | **58, 64, 70, 76, 82, 88, 94, 100 ± 3 days** | **104 ± 3 days** | | **108 4-weeks post-treatment ± 3 days** |
| Complete Physical Examination | X | - | - | - | X | - | - | X | X | X |
| Targeted Physical Examination | - | X | X | X | - | X | X | - | - | - |
| Vital Signs | X | X | - | Week 24 | - | Week 52 | Week 76 | X | X | X |
| Weight | X | - | - | Week 24 | - | - | - | X | X | X |
| Height | X | - | - | - | - | - | - | - | - | - |
| 12-Lead ECG | X | - | - | Weeks 4, 12, 24 | - | Week 52 | - | X | X | X |
| Hematology Laboratory | X | X | X | X | X | X | X | X | X | X |
| Chemistry Laboratory | X | X | X | X | X | X | X | X | X | X |





[redacted]

**Table 5: Table of Events (Continued)**

| | Screening Phase | 24-Week Double-Blind Placebo-Controlled Treatment Phase | | | 80-Week Active Treatment Extension Phase | | | | Early Termination Visit | Post-Treatment Observational Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit(s)[k]** | **1 Screening** | **2 Baseline[a]** | **3** | **4-9 Every 4 Weeks** | **10E** | **11E-17E Every 4 Weeks** | **18E-25E Every 6 Weeks** | **26E End of Treatment** | | **27E** |
| **Week(s)** | **-8 to -1** | **0** | **1 ± 3 days** | **4, 8, 12, 16, 20, 24 ± 3 days** | **25 ± 3 days** | **28, 32, 36, 40, 44, 48, 52 ± 3 days** | **58, 64, 70, 76, 82, 88, 94, 100 ± 3 days** | **104 ± 3 days** | | **108 4-weeks post-treatment ± 3 days** |
| PT and INR (for subjects receiving vitamin K antagonist [eg, warfarin] therapy, only)[b] | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | - | Weeks 32, 52 | Week 76 | X | X | X |
| Urine cytology | X | - | - | Weeks 12, 24 | - | Weeks 32, 52 | X | X | X | - |
| Urine β-hCG | - | X[c] | - | - | - | - | - | - | - | - |
| Serum β-hCG[d] | X | X | - | X | - | X | X | X | X | X |
| Pregnancy counseling for FCBP | X | X | X | X | X | X | X | X | X | X |
| **EFFICACY ASSESSMENTS** | | | | | | | | | | |
| HRCT[e] | X[f] | - | - | Week 24 | - | - | - | X[f] | X[f] | - |
| SGRQ | - | X | - | Weeks 12, 24 | - | - | - | X | X | - |

**Table 5: Table of Events (Continued)**

| | Screening Phase | 24-Week Double-Blind Placebo-Controlled Treatment Phase | | | 80-Week Active Treatment Extension Phase | | | | Early Termination Visit | Post-Treatment Observational Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit(s)[k]** | **1 Screening** | **2 Baseline[a]** | **3** | **4-9 Every 4 Weeks** | **10E** | **11E-17E Every 4 Weeks** | **18E-25E Every 6 Weeks** | **26E End of Treatment** | | **27E** |
| **Week(s)** | **-8 to -1** | **0** | **1 ± 3 days** | **4, 8, 12, 16, 20, 24 ± 3 days** | **25 ± 3 days** | **28, 32, 36, 40, 44, 48, 52 ± 3 days** | **58, 64, 70, 76, 82, 88, 94, 100 ± 3 days** | **104 ± 3 days** | | **108 4-weeks post-treatment ± 3 days** |
| [redacted] | | | | | | | | | | |
| Spirometry[g] | X | X | X | X | X | X | X | X | X | X |
| $SpO_2$ [g] | X | X | X | X | X | X | X | X | X | X |
| UCSD-SOBQ | - | X | - | Weeks 12, 24 | [redacted] | | | | | |
| $D_LCO$[g] | X | X | - | Week 24 | - | Week 52 | - | X | X | X |
| [redacted] | | | | | | | | | | |
| 6MWT with Borg Scale | X | X | - | Week 24 | - | Week 52 | Week 76 | X | X | X |
| Assessment for New or Worsening Shortness of Breath | X | X | X | X | X | X | X | X | X | X |





[redacted]

**Table 5: Table of Events (Continued)**

| | Screening Phase | 24-Week Double-Blind Placebo-Controlled Treatment Phase | | | 80-Week Active Treatment Extension Phase | | | | Early Termination Visit | Post-Treatment Observational Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit(s)[k]** | **1 Screening** | **2 Baseline[a]** | **3** | **4-9 Every 4 Weeks** | **10E** | **11E-17E Every 4 Weeks** | **18E-25E Every 6 Weeks** | **26E End of Treatment** | | **27E** |
| **Week(s)** | **-8 to -1** | **0** | **1 ± 3 days** | **4, 8, 12, 16, 20, 24 ± 3 days** | **25 ± 3 days** | **28, 32, 36, 40, 44, 48, 52 ± 3 days** | **58, 64, 70, 76, 82, 88, 94, 100 ± 3 days** | **104 ± 3 days** | | **108 4-weeks post-treatment ± 3 days** |
| [redacted] | | | | | | | | | | |
| **INVESTIGATIONAL PRODUCT (IP)** | | | | | | | | | | |
| Dispense IP[i] | - | X | X | X | X | X | X | X[j] | - | - |
| Return and Count IP | - | - | X | X | X | X | X | X | X | - |

Abbreviations: β-hCG = beta human chorionic gonadotropin; $D_LCO$ = diffusion capacity of the lung for carbon monoxide; E= Extension; ECG = electrocardiogram; FCBP= female of childbearing potential; HRCT = high resolution computed tomography; INR = international normalized ratio; IP = investigational product; IPF = idiopathic pulmonary fibrosis; [redacted] PT = prothrombin time; [redacted] SGRQ = St.





[redacted]

George's Respiratory Questionnaire; 6MWT = Six-minute Walk Test; $SpO_2$ = oxygen saturation; TB = tuberculosis; UCSD-SOBQ = University of California San Diego Shortness of Breath Questionnaire.

[a] The Baseline value is defined as the last assessment prior to or on the date of the first dose of IP in the study.
[b] PT and INR will only be done on those subjects who require monitoring for vitamin K antagonist levels (eg, warfarin).
[c] Urine pregnancy test will be performed to assess subject eligibility prior to the first administration of IP, if the initial serum pregnancy test did not already occur within 72 hours of dosing (negative results required for IP administration).
[d] Serum pregnancy testing during the 80-week Active Treatment Extension Phase occurs every 4 weeks for females of child bearing potential.
[e] HRCT used to qualify subjects for inclusion can be performed between Visits 1 and 2, inclusive, or can utilize historical HRCT images (within 18 months of randomization) which still require review by a central reader. For sites subject to regulatory restrictions that do not permit HRCT within this time period, a previous HRCT scan is permissible if the scan is deemed sufficient for centralized review.

[redacted]

[g] Spirometry, $D_LCO$, and pulse oximetry will be assessed as part of the safety assessments for those subjects who discontinue for progressive disease during the 24-Week Double-blind Placebo-controlled and 80-Week Active Treatment Extension Phases.

[redacted]

[i] Blinded IP will be packaged in 32 tablet-count, 16-day blister cards (16-day card includes IP for two additional days in the event the subject is unable to return for their scheduled visit).
- On Visits 2 and 3, one blister card will be dispensed to the subject. Remaining IP from the blister card issued on Visit 2 will be reissued to the subject along with a new card on Visit 3. The subject should be instructed to finish the remaining IP in the blister card issued at Visit 2 before starting the new blister card issued at Visit 3.
- On Visits 4 to 8, two blister cards will be dispensed to the subject per visit.
- On Visits 9 and 10E, one blister card will be dispensed to the subject. Remaining IP from the blister card issued on Visit 9 will be reissued to the subject along with a new card on Visit 10E. The subject should be instructed to finish the remaining IP in the blister card issued at Visit 9 before starting the new blister card issued at Visit 10E.
- On Visits 11E to 16E, two blister cards will be dispensed to the subject per visit.
- On Visit 17E to 24E, three blister cards will be dispensed to the subject per visit.
- On Visit 25E, two blister cards will be dispensed to the subject per visit.

[j] Final dose of IP administered at the investigative site.
[k] For all subsequent visits, an administrative window of ± 3 days is permitted. Scheduling of Visits 3 to 9 is based on Visit 2 (randomization date) and scheduling of Visits 10E to 26E is based on Visit 9 (re-randomization date). The Post-treatment Observational Follow-up Visit is scheduled 28 days (4 weeks) after the date of the last dose of IP ± 3 days.
[l] If a subject has adequate documentation of successful treatment for either latent or active TB, the QuantiFERON-TB Gold test is not needed. Instead, a chest radiograph, obtained within the 12 weeks prior to Screening or during Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, will be sufficient to permit further participation in the study for these subjects. Documentation of adequate treatment for TB must be obtained prior to randomization.

# 6. PROCEDURES

Any questions regarding the protocol should be directed to the Medical Monitor or designee.

Signed informed consent forms (ICFs) must be obtained before any study evaluations are performed and any samples are collected per local regulations during the course of the study.

## 6.1. Screening Phase

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 8 weeks after Screening (Visit 1) unless noted otherwise below. Subjects are permitted to be re-screened once should they fail to meet the study entry criteria; however, all re-screened subjects must be re-consented for the study.

*Note: Subjects who fail the entry criteria due to a positive hepatitis B, hepatitis C or TB test result should not be rescreened for the study. Subjects who received hepatitis B vaccination and who test positive for hepatitis B surface antibody and negative for both hepatitis B surface antigen and hepatitis B core antibody are not excluded from the study.*

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses will be performed by the contracted central laboratory. The central laboratory will provide a separate manual for the collection and processing of the samples for this study. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the Screening window, if necessary.

The following assessments will be performed at Screening as specified in the Table of Events, Table 5, after the informed consent has been obtained.

- The Screening Visit should be registered in the interactive web response system (IWRS).
- Demographics (eg, date of birth, sex, race, and ethnicity-if allowed by local regulations)
- Disease history, including specific information regarding diagnosis of IPF
- Complete Medical History: All relevant medical conditions diagnosed/occurring prior to Screening should be recorded, including smoking and alcohol history, as well as previous relevant surgeries.
- Prior Procedures: All procedures occurring up to 35 days prior to Screening Visit should be recorded.
- Prior and Current Medication Evaluation:
  - All IPF/PPF therapies used by the subjects should be recorded.
  - All medications (prescription and nonprescription, including vitamins) taken by the subject up to 35 days prior to Screening Visit should be recorded, including the stop dates for medications prohibited in the study. All medications taken by the subject at any time during the study must also be

recorded. Other key medications and therapies, such as previous treatment for tuberculosis or relevant diseases, should also be recorded.

Additional instructions can be found in the electronic case report form (CRF) Completion Guidelines.

- Washout of all disallowed therapies defined in Sections 4.3 and 8.2 if required should commence after the informed consent is signed on the initial day of Screening (Visit 1).
- Complete Physical Examination: Complete physical examinations will include evaluation of the skin, nasal cavities, eyes and ears, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. Gynecological, urogenital and rectal examinations will not be performed unless for cause.
- Vital Signs, Height and Weight: Vital signs, including body temperature, pulse rate, respiration rate, and seated blood pressure will be taken. Height and weight (to be done in street clothes, no shoes) will also be measured and recorded.
- 12-lead electrocardiogram (ECG): All ECG recordings will be manually over-read on an ongoing basis by a cardiologist at the core ECG laboratory for QT measurement and QTc calculation using Fridericia's formula (QTcF). The central cardiologist will interpret all ECGs with respect to PR interval, QRS duration, heart rate and R-R interval, QT and QTcF intervals and for arrhythmia, ischemia or any relevant finding. Details regarding the ECG recordings are described in a separate manual.
- Spirometry: Spirometry for FVC (volume of air that can forcibly be blown out after full inspiration) and $FEV_1$ (maximum volume of air that can forcibly be blown out in the first second during the FVC maneuver) will be performed at prespecified times. Sites are required to use the spirometry equipment provided by the Sponsor. Spirometers must meet the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (Miller, 2005).

  For each subject, all subsequent pulmonary function testing should start at approximately the same time of the day (in the morning with ±1 hour maximum difference; time will be recorded). Subjects must refrain from strenuous activity at least 12 hours prior to testing.

  Details of the procedure will be described in a separate manual.

  $D_LCO$: The $D_LCO$ will be measured at prespecified times. $D_LCO$ will be measured after the spirometry testing is completed. $D_LCO$ equipment will be calibrated centrally to meet ATS/ERS criteria (MacIntyre, 2005). The same tester should be employed during the study. Details of the procedure will be described in a separate manual.

  *Note: For data analysis, all $D_LCO$ values will be corrected for hemoglobin.*
- Pulse oximetry will be used to measure arterial oxygen saturation.

- Historical lung biopsy (surgical lung biopsy [SLB] or lung cryobiopsy) if used for study eligibility must be sent to the central pathologist selected by the Sponsor for expertise in the scoring of IPF-related histologic findings (Appendix G).
- Chest HRCT: For confirmation of diagnosis, chest HRCT is required for all subjects. HRCT may be obtained during screening or historical HRCT (within 18 months of randomization) may be used to qualify the subject for study entry. All HRCT images will be reviewed by a central reader. In the event a historical HRCT does not meet study eligibility (as determined by the central reader), a new HRCT must be obtained. For sites subject to regulatory restrictions that do not permit HRCT within this time period, a previous HRCT scan is permissible if the scan is deemed sufficient for centralized review. Diagnosis of IPF by HRCT and lung biopsy, if obtained, will be assessed according to Lynch, 2018 (Appendix G).

  Details regarding the analyses and handling of the HRCT images and historical lung biopsies for central reading will be provided in a separate manual.

  *Note: A new lung biopsy should not be obtained at the Screening Visit in order to qualify the subject for the study.*
- 6MWT: A 6MWT will be performed in accordance with the ATS guidelines (ATS, 2002) and as described in Appendix E. The 6MWT measures the distance a subject is able to walk on a hard, flat surface, over a total of six minutes. In conjunction with the 6MWT, the subject will also complete the Borg Scale (Appendix F), assesses dyspnea.
- Assessment for new or worsening shortness of breath.

The standard requirements to perform the above procedures will be outlined in the separate operations manual.

- The following laboratory specimens will be collected:
  - Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, WBC count (with differential), neutrophil count (percent and absolute), and platelet count
  - Chemistry panel will include albumin, alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]), alkaline phosphatase, aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT]), gamma-glutamyl transferase (GGT), bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, indirect bilirubin, total cholesterol, HDL, LDL, total protein, triglycerides, and uric acid.
  - Prothrombin time (PT) and international normalized ratio (INR) will be obtained only in those subjects receiving vitamin K antagonists (eg, warfarin).

- Urinalysis: semiquantitative testing via dipstick (specific gravity, pH, glucose, erythrocytes, leukocytes, protein, and nitrite) will be performed by the central laboratory. Microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the dipstick urinalysis is abnormal.

  *Note: If the Screening Visit 1 urinalysis test results are positive (eg, leukocyte esterase or nitrite present), a urine culture test is required and the subject must have a confirmatory negative urine culture test to rule out urinary tract infection (UTI) prior to randomization, which can be performed using the provided central laboratory urine culture kits or a local laboratory at the site.*

- In addition to the routine urinalysis, urine cytology will be done for the detection of abnormal cells. The urine cytology specimen will be evaluated by a pathologist at the central laboratory.

  *Note: "Abnormal, clinically significant" results should be recorded in the Medical History CRF if found prior to first dose of IP, or in the AE CRF if found after the first dose of IP. Clinical laboratory evaluations do not require subjects to be fasting. However, the site will record on the lab requisition form whether a clinical laboratory evaluation was obtained in the fasting or nonfasting state.*

- Mycobacterium tuberculosis (TB) testing: Testing will be done at the Screening Visit via QuantiFERON®-TB Gold.

  *Note: A positive QuantiFERON-TB Gold test or 2 successive indeterminate QuantiFERON-TB Gold tests will disqualify the subject from further participation in the study.*

  *Note: If a subject has adequate documentation of successful treatment for either latent or active TB, the QuantiFERON-TB Gold test is not needed. Instead, a chest radiograph, obtained within the 12 weeks prior to Screening or during Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, will be sufficient to permit further participation in the study for these subjects. Documentation of adequate treatment for TB must be obtained prior to randomization.*

- Viral tests: Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) testing: testing will be performed at Screening. The hepatitis screen includes testing for hepatitis B surface antigen and antibody, hepatitis B core antibodies (IgG/IgM), and antibodies to hepatitis C. A positive result for one or more of these tests will disqualify the subject from further participation in the study. The Investigator should refer the subject to his/her general practitioner or other appropriate healthcare provider for further follow-up.

  *Note: Subjects who received hepatitis B vaccination and who test positive for hepatitis B surface antibody and negative for both hepatitis B surface antigen and hepatitis B core antibody are not excluded from the study.*

  - Pregnancy test: Testing is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at the Screening Visit.

    *Note: Urine pregnancy test will be performed to assess subject eligibility prior to the first administration of IP, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration).*

  - Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.

  - Postmenopause test: Estradiol and follicle-stimulating hormone (FSH) levels are required for all females who have not had a menses for at least one year, and do not have documentation confirming their postmenopausal status.

[redacted]

- Adverse Events: Adverse event assessment begins when the subject signs the informed consent form and is assessed continuously throughout the study, until 28 days following the last dose of IP.

  All abnormal ECG, laboratory and physical exam findings identified during the Screening period will be captured on the medical history page of the CRF.

  Of note, minor fluctuations of symptoms (eg, cough and dyspnea) that reflect the underlying disease should not necessarily be recorded as an AE if they are similar in intensity and duration to prior such fluctuations. However, more marked and/or sustained worsening of such symptoms should be recorded as an AE.

  Refer to Section 10 for details pertaining to AEs. Adverse event assessment begins when the subject signs the informed consent form. If a subject is hospitalized for a serious adverse event, additional information will be collected regarding reason and duration of hospitalization and to which unit the subject was admitted.

- Information to be collected on Screening Failures: At a minimum, the information to be collected should include the informed consent date, demographics, and reason why the subject did not qualify for the study will be collected for all subjects determined to be screen failures. Adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed to be a screen failure. This information will be captured in the subject's source documents and appropriate CRF(s).

***Note:***

- *For purposes of study eligibility, inclusion and exclusion criteria/results should be reviewed again prior to randomization (Baseline [Visit 2]) to ensure the subject continues to meet criteria for entry into the study. Additionally, FVC must be repeated at the Baseline (Visit 2) and should be the first assessment done at that visit.*

- *If the subject does not receive IP within 8 weeks after Screening (Visit 1), the subject must be screen failed, and all screening assessments with the exception of*

*the HRCT, if previously done, must be repeated. Details on how to handle screen failures will be described in the CRF operations manual.*

## 6.2. Treatment Phase

The subject will begin treatment upon confirmation of eligibility at the Baseline (Visit 2). For all subsequent visits, an administrative window of ± 3 days is permitted. Scheduling of Visits 3 to 9 is based on Visit 2 (randomization date) and scheduling of Visits 10E to 26E is based on Visit 9 (re-randomization date).

The following evaluations will be performed at the frequency specified in the Table of Events, Table 5 and in the order described below. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Adverse event evaluation
- Concomitant medications reviewed with the subject
- Concomitant procedures reviewed with the subject
- Patient-reported outcome questionnaires will be completed as described in Section 6.7
- Assessment for new or worsening shortness of breath

As part of the routine assessments during the study visit, subjects will be assessed for new or worsening of shortness of breath (SOB). The Investigator should use his/her clinical judgement to decide how to further assess and treat such subjects.

[redacted]

Subjects who experience and receive adequate treatment for SOB with permitted drugs (see Section 8.1.2) but demonstrate further clinical decline and/or decrease of ≥ 10% from baseline in % predicted FVC at two consecutive evaluations at a minimum of 4 weeks between evaluations should discontinue IP and enter the 4-week Post-treatment Observational Follow-up Phase (Table of Events, Table 5). Whether to discontinue a subject from study treatment who experiences unexplained worsening in hypoxemia (an absolute decrease from baseline of 4% or more in $SpO_2$) will be left up to the Investigator's discretion. Treatment of subjects during the Post-treatment Observational Follow-up Phase is at the discretion of the Investigator.

All relevant clinical data (summary on clinical course, signs and symptoms; laboratory, lung function and imaging results; and treatment provided) relating to new or worsening shortness of breath must be collected by the Investigator. Changes in respiratory status that are considered by the Investigator as possibly or likely due to [redacted] disease progression will be reviewed further by the independent Adjudication Committee. Details regarding the adjudication process will be described in a separate charter.

- Efficacy assessments as described in Section 6.4

[redacted]

- 12-lead ECG will be performed as described in Section 6.1
- Complete/targeted physical examination (source documented only): Complete physical examinations will include evaluation of the skin, nasal cavities, eyes and ears, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. Gynecological, urogenital and rectal examinations will not be performed unless for cause.

  A targeted physical examination includes evaluation of the respiratory, cardiovascular, abdominal systems. Clinically significant abnormal findings identified during the physical examinations will be recorded on the CRF as adverse events. Gynecological, urogenital and rectal examinations will not be done unless for cause.
- Vital signs: Vital sign measurements (body temperature, pulse rate, respiration rate, and seated blood pressure) will be taken. If an abnormal (out of range) value constitutes an adverse finding, it should be reported as an AE if appropriate.
- Weight (to be done in street clothes, no shoes) will be measured and recorded.
- Clinical laboratory safety tests will be performed as described in Section 6.1, with the exception of those labs performed only at Screening (eg, QuantiFERON-TB Gold®, hepatitis test, and postmenopausal testing).

[redacted]

- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.
- Study IP dispensation (refer to Section 7.2 and the Table of Events, Table 5), returns (all used and unused blister cards) and IP compliance will be assessed.

A more detailed description of the order of the procedures for each visit will be provided in the operations manual.

### 6.2.1. End of Treatment

An end of treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table of Events, Table 5 and in the order described below:

- Adverse event evaluation
- Review of concomitant medications

- Review of concomitant procedures
- Patient-reported outcome questionnaires will be completed as described in Section 6.7
- Assessment for new or worsening SOB
- Efficacy assessments as described in Section 6.4

- 12-lead ECG as described in Section 6.1
- Complete physical examination (source documented only) in Section 6.1
- Vital signs as described in Section 6.2. All abnormal (out of range) value that constitutes an adverse finding (event), should be reported as an AE if appropriate
- Weight (to be done in street clothes, no shoes) will also be measured and recorded
- Clinical laboratory safety tests as described in Section 6.1, with the exception of those labs performed only at Screening (eg, QuantiFERON-TB Gold, hepatitis test, and postmenopausal testing)
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.

- Study IP returned (all used and unused blister cards) and IP compliance will be assessed

## 6.3. Post-treatment Observational Follow-up Phase

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1. The Post-treatment Observational Follow-up Visit is scheduled 28 days (4 weeks) after the date of the last dose of IP ± 3 days.

The following evaluations will be performed as specified in the Table of Events, Table 5 and in the order described below:

- Adverse event evaluation (monitored through 28 days after the last dose of IP or until the last study visit, whichever is longer).
- Concomitant medications reviewed with the subject
- Concomitant procedures reviewed with the subject
- Assessment for new or worsening SOB
- Pulmonary function tests (for safety only):


  - Spirometry ($FEV_1$, FVC)
  - $D_LCO$
  - Pulse oximetry
- 6MWT
- 12-lead ECG as described in Section 6.1
- Complete physical examination (source documented only). Refer to Section 6.1
- Vital signs including weight
- Clinical laboratory safety tests as described in Section 6.1, with the exception of those labs only performed only at Screening (eg, QuantiFERON-TB Gold, hepatitis test, and postmenopausal testing)
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted

## 6.4. Efficacy Assessment

Efficacy assessments should be performed in the order presented below.

### 6.4.1. Pulmonary Function Tests

Information regarding the potential effect of treatment on lung function, including FVC and $D_LCO$ will be collected. FVC and $D_LCO$ have been reported to correlate with survival in patients with IPF (Latsi, 2003; Collard, 2003; Flaherty, 2003; Noble, 2011; King, 2014).

#### 6.4.1.1. Spirometry

Spirometry will be measured as described in Section 6.1 and will be performed at multiple time points throughout the treatment phase of the study. Prior to spirometry testing, subjects must adhere to the washout periods indicated below if the following concomitant medications are being used:

- Short-acting bronchodilator: ≥ 8 hours
- Long-acting bronchodilator: ≥ 24 hours

For each subject, pulmonary function testing must occur at approximately the same time of day (in the morning with ±1 hour maximum difference, time will be recorded) relative to IP dosing in the clinic. On days of clinic visits (including the Screening Visit), subjects must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Spirometry will be the first physiologic efficacy assessment performed at each visit.

Details regarding the process and handling of the spirometric tests will be described in the separate operations manual.

#### 6.4.1.2. $D_LCO$

Evaluation of the $D_LCO$ will be done by a single breath $D_LCO$ according to task force recommendations (MacIntyre, 2005). The $D_LCO$, which represents carbon monoxide uptake

into the blood from a single inspiration in 10 seconds, will be measured at the same visits when spirometry is being assessed. *Note: in some regions throughout the world, $D_LCO$ is referred to as $T_LCO$ [transfer factor for carbon monoxide]. In this protocol, $D_LCO$ will be the only nomenclature used.* The $D_LCO$ will measure the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries. All sites will use their own calibrated equipment per taskforce recommendations for $D_LCO$. $D_LCO$ will be performed after the spirometry assessment is done. Details regarding the process and handling of the $D_LCO$ tests will be described in a separate operation manual.

*Note: For data analysis, all $D_LCO$ values will be corrected for hemoglobin.*

### 6.4.2. Pulse Oximetry

Pulse oximetry will be used to measure arterial oxygen saturation ($SpO_2$). Hypoxemia is a component of the definition of disease progression (Section 9.7.2). All sites will provide their own oximeter.

### 6.4.3. 6-Minute Walk Test

The 6MWT has been shown to be a predictor of mortality in IPF (Lederer, 2006; Caminati, 2009). Changes in the 6MWT demonstrate strong correlations with changes in lung function and quality of life (Nathan, 2015). Therefore, this measurement may be an important, clinically relevant outcome parameter in patients treated with CC-90001.

A 6MWT will be performed as described in Section 6.1.

[redacted]

### 6.4.5. Chest High-resolution Computed Tomography

- Eligibility HRCT for all subjects
  - Historical (obtained within 18 months of randomization visit) or a new HRCT will be obtained for study eligibility. In the event a historical HRCT is determined by the central reader as not meeting study eligibility, a new HRCT must be done.





[redacted]

*Note: For sites subject to regulatory restrictions that do not permit HRCT within this time period, a previous HRCT scan is permissible if the scan is deemed sufficient for centralized review.*

[redacted]

Details regarding the performance of HRCT will be described in the separate operations manual.

[redacted]





[redacted]

[redacted]

## 6.7. Patient-reported Outcomes

All questionnaires listed on the Table of Events, Table 5 will be completed by subjects using an electronic site pad. The SGRQ, UCSD-SOBQ [redacted] questionnaires are incorporated as endpoints in this study to assess the subjects' perception of how IPF affects their quality of life and to measure overall disease burden.

At each visit the subject will complete the SGRQ first, followed by the UCSD-SOBQ [redacted] before any other procedures. The person administering the questionnaires should check for completeness but should never help the subject in choosing a response. Subjects will not have access to any data collected, or the results of the previous questionnaires.

- St. George's Respiratory Questionnaire (Appendix B): The SGRQ is a quality of life health questionnaire that has been validated in IPF. It consists of 76 items in three domains:
  - Symptoms
  - Activity

– Impact of disease on daily life

A total score is calculated from 0 (no health impairment) to 100 (maximum health impairment). In addition to the total score, there is also a score for each domain: symptoms, activity, and impact which are scored 0-100.

- The University of California San Diego Shortness of Breath Questionnaire (Appendix C): The UCSD-SOBQ is a 24-item dyspnea questionnaire that asks subjects to rate themselves from 0 ("Not at all") to 5 ("Maximally or unable to do because of breathlessness") in two areas: 1) how short of breath they are while performing various activities (21 items); and 2) how much shortness of breath, fear of hurting themselves by overexerting, and fear of shortness of breath limit them in their daily lives (3 items). If the subject does not routinely perform the activity, they are asked to estimate the degree of shortness of breath anticipated. The UCSD-SOBQ is scored by summing responses across all 24 items to form a total score. Scores range from 0 to 120.





# 7. DESCRIPTION OF STUDY TREATMENTS

## 7.1. Description of Investigational Product(s)

CC-90001 will be supplied as film-coated 200 mg tablets by the Sponsor and labeled appropriately as IP for this study.

Applicable doses of CC-90001 will be provided as blinded 32 tablet-count, 16-day blister cards according to local clinical study agreement and in accordance with local guidelines. Please refer to the clinical label for more details on storage condition. CC-90001 is not approved for any indication. CC-90001 can be taken with or without food. The dosing schedule is described in Section 7.2.

## 7.2. Treatment Administration and Schedule

All IP treatment allocation will be handled via interactive web response system (IWRS).

**Subjects are instructed to take 2 tablets once daily, approximately the same time of day, with or without food.**

The IPF study subjects are provided with the following IP treatments:

- **24-week Double-blind, Placebo-controlled Treatment Phase: Baseline (Visit 2) to Week 24 (Visit 9)**

  Subjects will receive 2 tablets once daily as follows:

  – CC-90001 400 mg PO QD (two 200 mg tablets)

  – CC-90001 200 mg PO QD (one 200 mg tablet and one placebo tablet)

  – Placebo PO QD (two placebo tablets)

  *Note: The first dose of IP is taken on the day of Visit 2 and the last dose of IP is taken on the day of Visit 9.*

- **80-week Active Treatment Extension Phase: Week 24 + 1 Day (Day After Visit 9) to Week 104 (Visit 26E)**

  Subjects will receive 2 tablets once daily as follows:

  – CC-90001 400 mg PO QD (two 200 mg tablets)

  – CC-90001 200 mg PO QD (one 200 mg tablet and one placebo tablet)

  *Note: The first dose of IP is taken on the day after Visit 9 and the last dose is taken at Visit 26E.*

At Visit 9/Week 24, all IPF subjects originally randomized to placebo at baseline during the 24-week Double-blind Placebo-controlled Treatment Phase will be re-randomized 1:1 to receive blinded CC-90001 (200 mg or 400 mg PO QD) via IWRS during the 80-week Active Treatment Extension Phase. All subjects originally randomized to CC-90001 (200 mg or 400 mg PO QD) will remain on that same blinded treatment assignment. Subjects begin the blinded-dose active treatment the day after Visit 9 (ie, Week 24 + 1 day). During the 80-week Active Treatment Extension Phase, all subjects not on concurrent protocol-allowable

SOC therapy will have the opportunity, if deemed appropriate by the Investigator, to receive allowed SOC [redacted].

The PPF substudy subjects are provided with the following IP treatments:

- **24-week Double-blind, Placebo-controlled Treatment Phase: Baseline (Visit 2) to Week 24 (Visit 9)**

  Subjects will receive 2 tablets once daily as follows:

  – CC-90001 PO QD (400 mg PO QD [two 200 mg tablets], unless review of benefit-risk favors 200 mg PO QD)

  – Placebo PO QD (two placebo tablets)

  *Note: The first dose of IP is taken on the day of Visit 2 and the last dose of IP is taken on the day of Visit 9.*

- **80-week Active Treatment Extension Phase: Week 24 + 1 Day (Day After Visit 9) to Week 104 (Visit 26E)**

  Subjects will receive 2 tablets once daily as follows:

  – CC-90001 PO QD (400 mg PO QD [two 200 mg tablets], unless review of benefit-risk favors 200 mg PO QD)

  *Note: The first dose of IP is taken on the day after Visit 9 and the last dose is taken at Visit 26E.*

At Visit 9/Week 24, all PPF subjects originally randomized to placebo at baseline during the 24-week Double-blind Placebo-controlled Treatment Phase will receive blinded CC-90001 (400 mg PO QD, unless review of benefit-risk favors 200 mg PO QD) via IWRS during the 80-week Active Treatment Extension Phase. All subjects originally randomized to CC-90001 (400 mg PO QD, unless review of benefit-risk favors 200 mg PO QD) will remain on that same blinded treatment assignment. Subjects begin the blinded-dose active treatment the day after Visit 9 (ie, Week 24 + 1 day). During the 80-week Active Treatment Extension Phase, the decision for PPF subjects to receive additional treatments for pulmonary fibrosis [redacted] is at the discretion of the Investigator.

Blinded IP will be packaged in 32 tablet-count, 16-day blister cards. The 16-day blister cards include IP for two additional days in the event the subject is unable to return for their scheduled visit.

- On Visits 2 and 3, one blister card will be dispensed to the subject. Remaining IP from the blister card issued on Visit 2 will be reissued to the subject along with a new card on Visit 3. The subject should be instructed to finish the remaining IP in the blister card issued at Visit 2 before starting the new blister card issued at Visit 3.
- On Visits 4 to 8, two blister cards will be dispensed to the subject per visit.
- On Visits 9 and 10E, one blister card will be dispensed to the subject. Remaining IP from the blister card issued on Visit 9 will be reissued to the subject along with a new card on Visit 10E. The subject should be instructed to finish the remaining IP in the blister card issued at Visit 9 before starting the new blister card issued at Visit 10E.

- On Visits 11E to 16E, two blister cards will be dispensed to the subject per visit.
- On Visit 17E to 24E, three blister cards will be dispensed to the subject per visit.
- On Visit 25E, two blister cards will be dispensed to the subject.

### 7.2.1. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP (CC-90001) only. Therefore, for a drug to meet the overdose definition it must be both required and an IP. In this study the only required IP is CC-90001 and placebo, hence the overdose definition will apply to only CC-90001 (or matching placebo). Other required or optional non-IP intended for prophylaxis of certain side effects, to treat the disease, etc, are excluded from this definition. Overdose for this protocol is defined as ingestion of > 2 tablets within the same calendar day, whether by accident or intentionally. Adverse Events associated with an overdose must be collected on the Adverse Events page of the CRF for all overdosed subjects, but the overdose itself is not considered an AE.

Detailed information about any CC-90001 overdose in this study, regardless of whether the overdose was accidental or intentional, should be reported on the drug exposure CRF page.

### 7.2.2. Dose Modification/Interruptions

This is a dose-finding study therefore no dose reductions will be permitted. However, in the event the subject experiences a study drug-related adverse event, a temporary IP interruption for up to 4 days will be permitted anytime during the study. The Sponsor should be notified in advance of the dosage interruption; however, the decision to interrupt IP dosing will be based on the Investigator's clinical judgment. If the subject misses 4 or more consecutive days of dosing, Celgene must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study IP and enter the Post-treatment Observational Follow-up Phase.

If a dose of IP is missed, it should be taken as soon as possible on the same day, provided it occurs within 36 hours of the previous dose. The dose should be skipped if the timing of the dose occurs > 36 hours of the previous dose.

*Note: If the dose is missed for the entire day, the subject should not take an extra dose the next day or take an unscheduled dose.*

#### 7.2.2.1. Dose Interruptions for Planned Surgical Procedures

It is unknown if CC-90001 affects wound healing in humans. Subjects should interrupt IP 7 to 10 days prior to and restart 7 days after any surgical procedures.

### 7.2.3. Method of Treatment Assignment

An IWRS will be used to track IP assignments for all subjects and treatment groups through the 24-week Placebo-controlled Treatment Phase and 80-week Active Treatment Extension Phase.

## 7.3. Packaging and Labeling

The label(s) for IP will include the Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

## 7.4. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

## 7.5. Investigational Product Compliance

The Investigator(s) or designee(s) is responsible for accounting for all study IP that is issued to and returned by the subject during the course of the study. Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate section of the subject's CRF and source documents. Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. Investigational product will be dispensed as noted in the Table of Events, Table 5. The subjects will be instructed to return the IP containers, including any unused IP, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their IP as instructed at each study visit. Any problems with IP compliance will be reviewed with the subject. If the subject misses 4 or more consecutive days of dosing, Celgene must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study IP and enter the Post-treatment Observational Follow-up Phase.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 80% of the doses between study visits) should be discussed with Celgene. Compliance will be categorized into 4 classes: $< 50\%$, $\geq 50\%$ to $\leq 80\%$, $> 80\%$ to $\leq 120\%$, $> 120\%$.

IP compliance will be calculated at each visit as:

$$\text{Compliance (\%)} = \frac{\text{Number of tablets actually taken between visits}}{\text{Number of tablets that should have been taken between visits}} \times 100$$





[redacted]

# 8. CONCOMITANT MEDICATIONS

Over the course of this study, additional medications may be required to manage aspects of the disease state of a subject, including side effects from treatments or progressive disease. All medications (prescription and non-prescription), treatments, and therapies taken by the subject from Screening throughout his/her entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the CRF. The dose, unit, frequency, route, indication, date the medication was started, and date the medication was stopped (if not ongoing) must be recorded.

## 8.1. Permitted Concomitant Medications

### 8.1.1. Permitted Concomitant Medications Throughout the Entire Study

Subjects may take any medication that is not restricted by the protocol and would not be expected to interfere with the conduct of the study. Chronic medication should be dosed on a stable regimen throughout the study.

- Subjects in the concurrent protocol-allowable SOC therapy group must be receiving the same dose of medication for IPF at least 8 weeks prior to Screening Visit 1 and through Visit 9/Week 24. [redacted]
- During the 80-week Active Treatment Extension Phase, all subjects not on concurrent protocol-allowable SOC therapy will have the opportunity, if deemed appropriate by the Investigator, to receive allowed SOC [redacted].
- Oral corticosteroid(s) at stable dose ≤ 12.5 mg/day prednisone or equivalent will be permitted throughout the study. Inhaled corticosteroids at approved doses will be permitted throughout the study.
- The following commonly used products are acceptable for use during the study: acetaminophen (≤ 3 grams/day), ibuprofen, naproxen sodium, NSAIDs, loratadine, pseudoephedrine, guaifenesin, calcium, histamine-receptor antagonists, proton-pump inhibitors, antidepressants, and hypertension drugs.
- Supplemental oxygen is permitted as indicated (eg, new or worsening SOB, etc).
- Subjects may take statins (HMG-CoA reductase inhibitors) on the study however will require careful monitoring. To ensure the safety of the subjects, statins will be dose adjusted to an appropriate therapeutic level while being taken during the study (Section 8.2.1).
- Bronchodilators:
  - Short-acting bronchodilator may be used provided it does not occur within 8 hours of the study visit.
  - Inhaled long-acting bronchodilator may be used provided it does not occur within 24 hours of the study visit

- All medications required to treat adverse events or medical emergencies that occur throughout the study are permitted (eg, antibiotics).

### 8.1.2. Permitted Medications to Treat New or Worsening Shortness of Breath

Medications, such as prednisone (> 12.5 mg/day or equivalent), azathioprine, and cyclophosphamide can be initiated or increased at Investigator's discretion for the treatment of an exacerbation. Subjects may be given supplemental oxygen to alleviate hypoxemia. These drugs should be discontinued at the Investigator's discretion upon resolution of the exacerbation. If an exacerbation has not improved within 6 weeks or a subject has shown signs of further clinical decline despite adequate treatment, the subject should be discontinued from study IP and enter the Post-treatment Observational Follow-up Phase, as per the Table of Events, Table 5.

### 8.1.3. Permitted Concomitant Medications Only During the 80-Week Active Treatment Extension Phase

For subjects not in the SOC group, an antifibrotic therapy that is considered by the country/Investigator as SOC [redacted] will be permitted after Week 24 [redacted].

## 8.2. Medications that Require Careful Monitoring

High doses of CC-90001 may moderately induce CYP3A4. Subjects receiving drugs that utilize this enzyme in their metabolic pathway (eg, warfarin) should be closely monitored during co-administration. All subjects receiving vitamin K antagonists (eg, warfarin) should be carefully monitored for changes in INR.

CC-90001 may inhibit the transporters P-gp, BCRP, OAT3, OATP1B1, OATP1B3, and OCT2 [redacted]. Drugs considered to be substrates of these transporters should be closely monitored for potential drug interactions while subjects are participating in the study. Additional substrates of these transporters can be found in Appendix H. Questions regarding potential co-administration of CC-90001 and drugs that are substrates for these transporters should be discussed with the Sponsor.

### 8.2.1. Statins

Due to the potential for DDIs, the following must be done to ensure the safety of subjects taking statins while on the study:

- During the Screening phase of the study, all subjects receiving statins should be prescribed the lowest approved statin dose for adults approximately 1 week before Visit 2 (Baseline). For example, a subject receiving atorvastatin 20 mg during the Screening Period should be instructed to begin taking atorvastatin 10 mg, instead, approximately 1 week prior to randomization.

  *Note: Subjects who are already receiving the lowest approved statin dose for adults should remain on that dose.*

- At Visit 2 (Baseline), eligible subjects will begin treatment with CC-90001. Following multiple oral doses of CC-90001, the steady state should be achieved on approximately Day 5.
- At Visit 3, the lipid profile will be assessed. Based on results of the subjects' lipid profile at Visit 3, the statin dose may be increased to the next highest approved dose, if indicated.

  *Note: If the lipid profile at Visit 3 is comparable to the lipid profile from Visit 1 (Screening), the statin dose should not be increased.*
- At Visit 4, the lipid profile will be assessed. Based on the subjects' lipid profile at Visit 4, the statin dose may be increased to the next approved dose, if indicated.

  *Note: If the lipid profile at Visit 4 is comparable to the lipid profile from Visit 1 (Screening), the statin dose should not be increased.*

The Investigator should use his/her clinical judgement to decide when/if the further increase in the statin dose is warranted and how to assess these subjects. **In particular, Investigators should monitor closely for AEs associated with increased statin exposures (eg, myalgia, liver function test abnormalities).** If needed, the Investigator should refer the subject to his/her general practitioner or other appropriate healthcare provider for further follow-up.

## 8.3. Prohibited Concomitant Medications

### 8.3.1. Prohibited Medications Throughout the Entire Study

The following medications cannot be administered for the specified times prior to the initiation of study IP and for the duration of the study.

- [redacted]
- Use of any cytotoxic/immunosuppressive agent including azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, cyclosporine, oral corticosteroids whose dose exceeds > 12.5 mg/day (prednisone or equivalent).

  *Note: Medications, such as prednisone (> 12.5 mg/day or equivalent), azathioprine, and cyclophosphamide can be initiated or increased at Investigator's discretion for the treatment of new or worsening shortness of breath (an exacerbation as described above [Section 8.1.2]).*
- Use of any cytokine modulators/biologics, such as etanercept, adalimumab, efalizumab, infliximab, or rituximab within 12 weeks of randomization.
- Use of any medications associated with hepatotoxicity risk, such as, but not limited to, acetaminophen > 3 grams/day and niacin > 2 grams/day while on study or within 2 weeks of first study dose.
- Use of marijuana within 3 months of Screening and during the study.

[redacted]

*Note: Drugs considered to be substrates of these transporters and without a narrow therapeutic index (eg, OATP1B1/3 substrates statins, OCT2 substrate metformin [Section 8.2.1]) should be closely monitored for potential drug interactions while subjects are participating in the study. Additional substrates of these transporters can be found in Appendix H.*

Exceptions may be made if, in the opinion of the Investigator, the medication [redacted] is needed to support best medical practice in the time frame of study participation AND such medication will not interfere with subject safety or the interpretation of study results. In such instances, the Sponsor's Medical Monitor and Investigator must concur.

### 8.3.2. Prohibited Medications During the 24-week Double-blind Placebo-controlled Treatment Phase

The following medications cannot be administered for the specified times prior to the initiation of study IP and for the duration of the 24-week Double-blind Placebo-controlled Treatment Phase of the study. Subjects taking the following medications must adhere to the following minimum washout period:

- Medications to treat IPF/PPF including, but not limited to, [redacted] D-penicillamine, endothelium receptor antagonists (eg, bosentan, ambrisentan), interferon gamma-1b, imatinib mesylate, and N-acetylcysteine [NAC], within 4 weeks prior to Screening Visit 1 and through Visit 9/Week 24.

## 8.4. Required Concomitant Medications

There are no required concomitant medications for inclusion in this study. [redacted]

# 9. STATISTICAL CONSIDERATIONS

## 9.1. Overview

This is a double-blind, randomized, placebo-controlled study with two treatment arms of oral CC-90001 (200 mg or 400 mg PO QD), or one treatment arm in the PPF substudy, compared to placebo. This study consists of a 24-week Double-blind Placebo-controlled Treatment Phase, an 80-week Active Treatment Extension Phase, and a 4-week Post-treatment Observational Follow-up Phase. The primary efficacy analysis of percentage point difference in the percent predicted FVC at Week 24 and the secondary analyses will be performed after all IPF subjects complete the 24-week Double-blind Placebo-controlled Treatment Phase (Weeks 0 to 24) or terminate early prior to the Week 24 visit, and similarly but separately for the PPF subjects. Additional analyses will also be performed after the final database lock when all subjects complete the study or terminate early. This section outlines the statistical analysis strategy and details will be documented in a separate Statistical Analysis Plan (SAP) prior to unblinding of the treatment assignments for the 24-week Double-blind Placebo-controlled Treatment Phase of the study. The randomization schedule will be generated and implemented by the IWRS vendor.

## 9.2. Study Population Definitions

The safety population will include all randomized subjects who received at least one dose of IP. The analysis of safety data in this study will be based on the safety population and subjects will be included in the treatment group they actually received.

The Full Analysis Set (FAS) will include all randomized subjects who received at least one dose of IP. The analysis of efficacy data in this study will be primarily based on the FAS and subjects will be included in the treatment group to which they are randomized.

The Per Protocol (PP) population will include all randomized subjects who received at least one dose of IP, have Baseline (Visit 2) and at least one post-Baseline FVC evaluation, and have no important protocol deviation during the 24-week Double-blind Placebo-controlled Treatment Phase. The final determination of important protocol deviation criteria will be made prior to the unblinding of the database and will be separately documented.

The FAS and PP populations will be analyzed separately for the IPF study and the PPF substudy.

## 9.3. Sample Size and Power Considerations

The primary objective of the study is to estimate the effect of CC-90001 in subjects with IPF either not receiving SOC or currently receiving SOC.

Approximately 165 subjects (55 subjects for CC-90001 200 mg ± SOC, 55 subjects for CC-90001 400 mg ± SOC, and 55 subjects for placebo ± SOC) provides 75% power for testing an overall difference of 2.2 percentage points in the Week 24 mean change from Baseline of percent predicted FVC value between either active treatment group ± SOC and the placebo group ± SOC (two-sided t-test; $\alpha = 0.1$; standard deviation [SD] = 5%), assuming that approximately 45% of subjects will be receiving concurrent protocol-allowable SOC based on the projected enrollment. The group size estimate is based on an assumed treatment

difference of 3 in percent predicted FVC in the non-SOC cohort and 1.3 in percent predicted FVC in the SOC cohort at Week 24 from Baseline. The study will also estimate the effect of CC-90001 in the PPF cohort.

## 9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

## 9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent by study phase. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

## 9.6. Efficacy Analysis

### 9.6.1. Analysis of the Primary Efficacy Endpoint for the IPF Study

A mixed-effect model of repeated measures (MMRM) will be used as the method for the primary efficacy analysis. The MMRM model will use the percent predicted FVC value as the dependent variable.

The MMRM model will include dose, time on treatment, current SOC (Yes/No), and interactions as fixed effects covariates. The model will also include the stratification factor applied to the non-SOC cohort, previous exposure to either pirfenidone or nintedanib (Yes/No), and Baseline percent predicted FVC value as fixed effects covariates. Time will be treated as a categorical variable in the MMRM model and will be considered as a repeated effect.

All post-baseline measurements up to Week 24 of percent predicted FVC values will be included in this analysis with no imputation of missing data other than that inherent in the MMRM model.

In addition to point estimates, 95% confidence intervals (CIs) for the differences calculated from the model (overall active treatment minus overall control, or active versus control within each cohort) of the least squares (LS) mean change from Baseline percent predicted FVC value and nominal p-values will also be provided, separately for each dose versus placebo comparison and also combining the 200 and 400 mg doses versus placebo comparison if both active treatment groups demonstrate efficacy. P-values and 95% CIs are considered descriptive measures of strength of association between dose and endpoint, rather than formal criteria to claim statistical significance.

In addition to the primary efficacy analysis of MMRM, non-parametric analysis of Rank-ANCOVA (Stokes, 2000) with a baseline FVC as a covariate for pair-wise comparisons with imputation of percent predicted FVC value for deaths to the worst rank will be applied as a

sensitivity analysis for the primary endpoint. Non-death discontinuation will be imputed in a different scheme; the details of the methods will be specified in the Statistical Analysis Plan.

To determine whether the treatment effect is consistent across various subgroups, the primary endpoint will be summarized by category of some classification variables observed at baseline including variables based on FVC (% predicted), age, time since first diagnosis of IPF, and prior therapy.

No multiplicity adjustment is planned for this study.

In addition to the above primary method of analysis on the primary endpoint, a Bayesian posterior probability that the effect ratios are greater than 1 (transformed on the log scale), within the naïve cohort and the SOC cohort separately, will be calculated using priors built from the current literature. The information from the literature may allow for a more precise estimate of the treatment effects.

[redacted]

### 9.6.2. Analysis of Secondary Efficacy Endpoints

#### 9.6.2.1. 24-Week Double-blind Placebo-controlled Treatment Phase

Descriptive statistics for change from Baseline, frequencies, or median time to event in efficacy measures will be summarized by visit for each treatment group, and for the treatment difference between each CC-90001 treatment group ± SOC and the placebo treatment group ± SOC. In addition, 95% CIs for the treatment differences will be provided to indicate the variability.

The analysis of most of the continuous secondary efficacy endpoints during the Double-blind Placebo-controlled Treatment Phase will be performed using an MMRM model in a manner similar to the primary analysis as specified in Section 9.6.1.

A random coefficient mixed effect model will be used to analyze the rate of decline of FVC. The usual FVC predictors, such as age, sex, height, and race, along with treatment and time interaction, will be included as fixed effects in the model, in which time will be treated as a numerical variable. In addition, intercept and slope of the linear relationship between FVC and time will be assumed to be subject-specific and treated as random coefficients. Comparisons of mean yearly decrease of FVC between treatment groups will be performed using appropriate contrasts.

A Cochran-Mantel-Haenszel (CMH) test will be used for the pair-wise comparisons of the proportions of subjects who experience disease progression at Week 24 between the two active treatment groups ± SOC and the placebo ± SOC. For the time to even data, such as time-to-first acute exacerbation and time to disease worsening, log-rank test will be provided by treatment, and a Kaplan-Meier estimate for the survival function will be provided for all the time to event data. For the time to event data (on-treatment time to death endpoint, time to first acute exacerbation and time to disease worsening while on treatment), Kaplan-Meier estimates for the survival function will be provided by treatment groups (CC-90001 200 mg PO QD ± SOC, CC-90001 400 mg PO QD ± SOC, and placebo ± SOC). The number and

percentage of events within different time intervals during treatment will also be provided by treatment group.

[redacted]

#### 9.6.2.2. 80-Week Active Treatment Extension Phase

Efficacy analyses for the 80-week Active Treatment Extension Phase will be performed based on subjects who received at least one dose of active treatment (200 mg PO QD or 400 mg PO QD) during the 80-week Active Treatment Extension Phase. The efficacy endpoints will be summarized with descriptive statistics by treatment group. Continuous efficacy endpoints will be summarized using mean, SD, median, minimum, maximum, and number of observations analyzed. Binary efficacy endpoints will be summarized with counts, percentages, and associated 95% CIs for the percentages within each treatment group based on Clopper-Pearson method.

[redacted]

## 9.7. Safety Analysis

The safety analyses for the 24-week Double-blind Placebo-controlled Treatment Phase will be performed using the safety population as defined in Section 9.2 by treatment group. The safety analyses will also be performed for the CC-90001 exposure period for subjects who receive at least one dose of CC-90001, which will include safety data during the 24-week Double-blind Placebo-controlled Treatment Phase and the 80-week Active Treatment Extension Phase. Safety will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements; summary of safety parameters will include data collected at scheduled, unscheduled, and early termination visit, and post-treatment observational follow-up visit. No inferential testing for statistical significance will be performed.

Adverse events will be classified using the MedDRA classification system. All AEs will be summarized by frequency, severity and relationship to IP. Adverse events leading to death or to discontinuation from treatment and serious adverse events will be listed separately. Study drug-related AEs will be listed separately. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory data will be summarized by visit descriptively (count, mean, median, standard deviation, and range). In addition, shift tables showing the number of subjects with values below, within and above the normal ranges pretreatment versus post treatment, together with the number determined to be clinically significant, will be provided.

Vital sign measurements, including weight, will be summarized descriptively by visit (count, mean, median, standard deviation, and range).

[redacted]

### 9.7.2. Disease Progression

A subject will have met the criteria for disease progression when one or more of the following events have occurred:

- Death from respiratory failure, or
- Absolute decrease of ≥ 10% from baseline in percent predicted FVC at two consecutive evaluations at a minimum of 4 weeks between evaluations, or
- Decrease from baseline of ≥ 50 meters in 6MWT distance (in the absence of a readily explainable cause, such as injury or trauma), or
- Unexplained worsening hypoxemia (an absolute decrease from baseline of 4% or more in $SpO_2$).

Subjects who experience an absolute decrease of ≥ 10% from baseline in percent predicted FVC at two consecutive evaluations at a minimum of 4 weeks between evaluations must be discontinued from the study IP and enter the Post-treatment Observational Follow-up (see Section 11.1). Example: a subject whose FVC decreases from 50% predicted at Visit 2 to 40% predicted at Visits 4 and 5 must be discontinued from the study. Whether to discontinue a subject from study treatment who experiences: 1) a decrease from baseline of ≥ 50 meters in 6MWT distance (in the absence of a readily explainable cause, such as injury or trauma), or 2) a new or worsening hypoxemia (an absolute decrease from baseline of 4% or more in $SpO_2$), is at the Investigator's discretion.

## 9.8. Interim Analysis

An initial interim analysis will be conducted after approximately 50 non-SOC subjects with IPF have completed 24 weeks of treatment. The purpose of this interim analysis is to

determine whether to terminate the study based on futility criteria and if futility criteria are not met, whether to discontinue any treatment group. Sample size re-estimation may be performed based on observed standard deviation and effect size.

If the safety and efficacy of CC-90001 from these initial IPF subjects are favorable, the study will continue as planned and enrollment into the PPF substudy will be initiated. Subjects enrolled into the PPF substudy will be randomized to CC-90001 400 mg PO QD, unless review of benefit-risk favors 200 mg PO QD, or placebo.

An additional unblinded interim analysis is planned after approximately 40 SOC IPF subjects have completed 24 weeks of treatment. The purpose of the additional interim analysis is to evaluate safety, tolerability and efficacy of CC-90001 in SOC IPF subjects, along with all study subjects enrolled into the study, and to determine if any treatment group should be discontinued. Sample size re-estimation may also be considered for the non-SOC group, the SOC group or subjects in the PPF sub-study.

If a decision at an interim analysis is made to discontinue a treatment group, that decision may be made separately for IPF subjects not receiving concurrent SOC and for IPF subjects receiving concurrent SOC. A decision to discontinue a treatment group will be based on lack of efficacy (ie, futility) and/or lack of acceptable safety and tolerability. If a treatment group is discontinued, subjects may receive a different CC-90001 dose regimen during the 80-week Active Treatment Extension Phase than during the 24-week Double-blind Placebo-controlled Phase.

Additional interim analyses may be conducted.

The DMC will be responsible for review of the interim analyses data and will make recommendations to a Celgene internal review committee, who will be responsible for final decision-making. The Celgene internal review committee members will not play a role in the study conduct and the blind will be maintained for persons responsible for the ongoing conduct and management of the study.

The details of these analyses, similar to analyses described in Sections 9.6.1 and 9.6.2, will be documented in a separate charter/analysis plan.

## 9.9. Other Topics

### 9.9.3. Analysis of Dose-Response

The primary method of analysis of dose-response for efficacy will be based on the MMRM model of the primary endpoint as described in Section 9.6.1. Supportive analyses, including sensitivity analyses and analyses of secondary endpoints, as described in Section 9.6.2, will also help inform optimal dose selection. The overall benefit-risk profile for each dose will be used to determine the dose(s) selected for further clinical development.

### 9.9.4. External Data Monitoring Committee

Although the Celgene study staff will monitor safety on an ongoing basis throughout the study, formal unblinded safety and efficacy assessments of the study data will be performed by an independent external DMC. The DMC is comprised of independent physician experts and a statistician who are not affiliated with the Sponsor and for whom there is no identified conflict of interest. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC charter.

The DMC will be also responsible for review of the interim analyses data and will make recommendations to a Celgene internal review committee (IRC), who will be responsible for final decision-making. The Celgene IRC members will not play a role in the study conduct and the blind will be maintained for persons responsible for the ongoing conduct and management of the study. The details of this analysis including the scope of distribution will be documented in a separate charter/analysis plan.

### 9.9.5. Celgene Safety Management Team

In addition to safety monitoring conducted by Investigators, site study personnel, and by the Celgene study team, blinded study safety data will be reviewed by the Celgene SMT. The SMT is comprised of lead representatives from multiple Celgene functions engaged in the CC-90001 development program.

# 10. ADVERSE EVENTS

## 10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-90001 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

## 10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

### 10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;

- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from Baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

### 10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

**Mild**

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated

- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

**Moderate**

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities.
- Drug therapy may be required

**Severe (could be non-serious or serious)**

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

### 10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

| | |
|---|---|
| Not suspected: | a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event. |
| Suspected: | there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event. |

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

### 10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

### 10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

### 10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to Baseline), recovered with sequelae, or death (due to the SAE).

## 10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

## 10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will follow up with the clinical investigator each trimester

of pregnancy and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

### 10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

### 10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

## 10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP or until the last study visit, whichever is longer), or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

### 10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

## 10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-90001 based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Events of disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

**Celgene Drug Safety Contact Information:**

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.





[redacted]

# 11. DISCONTINUATIONS

## 11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- Adverse event
- Withdrawal by subject
- Disease progression
- Acute exacerbation (has not improved within 6 weeks of treatment or the subject has shown evidence of further clinical decline despite appropriate treatment)
- Death
- Lost to follow-up
- Lung transplantation
- Other, to be specified on the CRF (eg, noncompliance, important protocol deviation)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

## 11.2. Discontinuation Criteria for Elevation of Hepatic Transaminases

Subjects should be carefully monitored for changes in liver function:

- ALT > 3 × upper limit of normal (ULN)
- AST > 3 × ULN

A history of alcohol use and or biliary colic as potential causes of the above findings should be elicited. For subjects experiencing either of the above, use of IP should be interrupted and subjects should undergo repeat testing, including ALT, AST, total bilirubin, and alkaline phosphatase, within 48 to 72 hours of the original test to confirm or refute the finding. If the ALT or AST lab result(s) is confirmed to be > 3 x ULN, the subject should not be re-challenged with IP. The subject should be discontinued from the study IP and enter the 4-week Post-treatment Observational Follow-up Phase and hepatic enzyme(s) should be followed until resolution.

## 11.3. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Lung transplantation
- Other, to be specified on the CRF (eg, noncompliance, important protocol deviation)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.





# 12. EMERGENCY PROCEDURES

## 12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

*Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.*

## 12.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the Interactive Web Response System (IWRS).

# 13. REGULATORY CONSIDERATIONS

## 13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

## 13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

## 13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

## 13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

## 13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

## 13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the

members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

## 13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

## 13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons, such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

# 14. DATA HANDLING AND RECORDKEEPING

## 14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

## 14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

## 14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the Clinical Trial Agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

## 15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

## 15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

## 15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant

risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted].

# 16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.





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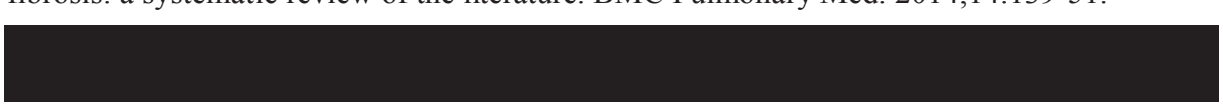

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# 18. APPENDICES

## Appendix A: Table of Abbreviations

**Table 6: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ADL | Activity of daily life |
| AE | Adverse event |
| [redacted] | |
| ALT | Alanine aminotransferase (SGPT) |
| AST | Aspartate aminotransferase (SGOT) |
| ATS | American Thoracic Society |
| [redacted] | |
| BAL | Bronchoalveolar lavage |
| BCRP | ATP Binding Cassette Protein G2 /ABCG2 |
| β-hCG | Beta-subunit of human chorionic gonadotropin |
| BID | Twice daily |
| [redacted] | |
| CBC | Complete blood count |
| [redacted] | |
| CI(s) | Confidence interval(s) |
| [redacted] | |
| $C_{max}$ | Maximum plasma concentration of drug |
| CMH | Cochran-Mantel-Haenszel |

# Appendix A: Table of Abbreviations (continued)

**Table 6: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| CRF | Case report form |
| [redacted] | |
| CYP | Cytochrome p450 |
| [redacted] | |
| $D_LCO$ | Diffusion capacity of the lung for carbon monoxide |
| DMC | Data Monitoring Committee |
| DVT | Deep vein thrombosis |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EEA | European Economic Area |
| EOT | End of treatment |
| [redacted] | |
| ERS | European Respiratory Society |
| ETC | Et cetera |
| FAS | Full analysis set |
| FCBP | Females of childbearing potential |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced exhaled volume in 1 second |
| [redacted] | |
| FSH | Follicle-stimulating hormone |
| FVC | Forced vital capacity |
| GCP | Good Clinical Practice |
| GD | Gestation Day |
| GGT | Gamma-glutamyltransferase |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| HDL | High density lipoprotein |
| HIV | Human immunodeficiency virus |

# Appendix A: Table of Abbreviations (continued)

**Table 6: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| HRCT | High resolution computed tomography |
| IB | Investigator's Brochure |
| $IC_{50}$ | 50% inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| [redacted] | |
| ILD | Interstitial lung disease |
| IND | Investigational New Drug |
| INR | International normalized ratio |
| IP | Investigational product |
| IPF | Idiopathic pulmonary fibrosis |
| IRB | Institutional Review Board |
| IRC | Internal review committee |
| [redacted] | |
| IWRS | Interactive web response system |
| JNK | c-Jun N-terminal kinase |
| [redacted] | |
| LDL | Low density lipoprotein |
| [redacted] | |
| LS | Least squares |
| MAD | Multiple ascending dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMP | Matrix metalloproteinase |
| MMRM | Mixed-effect model of repeated measures |
| MS | Millisecond |
| NAC | N-acetylcysteine |

# Appendix A: Table of Abbreviations (continued)

**Table 6: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| NOAEL | No observed adverse effect level |
| [redacted] | |
| OATP1B1 | Organic anion transporting polypeptide 1B1 |
| OATP1B3 | Organic anion transporting polypeptide 1B3 |
| OCT2 | Organic cation transporter 2 |
| [redacted] | |
| PD | Pharmacodynamics |
| PE | Physical examination or pulmonary embolism |
| [redacted] | |
| P-gp | P-glycoprotein |
| Phospho-c-Jun | Phosphorylated (Ser 63) c-Jun |
| PIN | Personal identification number |
| PK | Pharmacokinetics |
| PO | Per os (oral or orally) |
| PP | Per-protocol |
| PPF | Progressive pulmonary fibrosis |
| [redacted] | |
| QD | Quoque die (once a day or once daily) |
| QTcB | QTc calculation using Bazett's formula |
| QTcF | QTc calculation using Fridericia's formula |
| RBC | Red blood cell count |
| [redacted] | |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| [redacted] | |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |

# Appendix A: Table of Abbreviations (continued)

**Table 6: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| SGRQ | St. George's Respiratory Questionnaire |
| 6MWT | Six-minute walk test |
| SLB | Surgical lung biopsy |
| SOB | Shortness of breath |
| SOC | Standard of care |
| SOP | Standard operating procedure |
| $SpO_2$ | Arterial oxygen saturation by pulse oximetry |
| SP | Surfactant protein |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{1/2}$ | Half-life |
| TB | Tuberculosis |
| TEAE | Treatment-emergent adverse event |
| [redacted] | |
| UCSD-SOBQ | University of California San Diego Shortness of Breath Questionnaire |
| UIP | Usual interstitial pneumonia |
| ULN | Upper limit of normal |
| USA | United States of America |
| UVB | Ultraviolet B |
| VC | Vital capacity |
| WBC | White blood cell count |
| ± | With or without |





[redacted]

# Appendix B: St. George's Respiratory Questionnaire

## St. George's Respiratory Questionnaire
### PART 1

***Please describe how often your respiratory problems have affected you over the past 4 weeks.***

Please check (✓) *one box for each question*:

| | almost every day | several days a week | a few days a month | only with respiratory infections | not at all |
|---|---|---|---|---|---|
| 1. Over the past 4 weeks, I have coughed: | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Over the past 4 weeks, I have brought up phlegm (sputum): | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Over the past 4 weeks, I have had shortness of breath: | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Over the past 4 weeks, I have had wheezing attacks: | ☐ | ☐ | ☐ | ☐ | ☐ |

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
*(Go to Question 7 if you did not have a severe attack)*

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

# Appendix B: St. George's Respiratory Questionnaire (SGRQ) (Continued)

## St. George's Respiratory Questionnaire
**PART 2**

**Section 1**

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

**Section 2**

***These are questions about what activities usually make you feel short of breath <u>these days.</u>***

For each statement please check (✓) ***the box*** that applies to you ***these days***:

| | True | False |
|---|---|---|
| Sitting or lying still | ☐ | ☐ |
| Washing or dressing yourself | ☐ | ☐ |
| Walking around the house | ☐ | ☐ |
| Walking outside on level ground | ☐ | ☐ |
| Walking up a flight of stairs | ☐ | ☐ |
| Walking up hills | ☐ | ☐ |
| Playing sports or other physical activities | ☐ | ☐ |

# Appendix B: St. George's Respiratory Questionnaire (SGRQ) (Continued)

## St. George's Respiratory Questionnaire
### PART 2

**Section 3**

***These are more questions about your cough and shortness of breath <u>these days</u>.***

| | For each statement please check (✓) ***the box*** that applies to you ***these days***: True | False |
|---|---|---|
| Coughing hurts | ☐ | ☐ |
| Coughing makes me tired | ☐ | ☐ |
| I am short of breath when I talk | ☐ | ☐ |
| I am short of breath when I bend over | ☐ | ☐ |
| My coughing or breathing disturbs my sleep | ☐ | ☐ |
| I get exhausted easily | ☐ | ☐ |

**Section 4**

***These are questions about other effects that your respiratory problems may have on you <u>these days</u>.***

| | For each statement, please check (✓) ***the box*** that applies to you ***these days***: True | False |
|---|---|---|
| My cough or breathing is embarrassing in public | ☐ | ☐ |
| My respiratory problems are a nuisance to my family, friends or neighbors | ☐ | ☐ |
| I get afraid or panic when I cannot catch my breath | ☐ | ☐ |
| I feel that I am not in control of my respiratory problems | ☐ | ☐ |
| I do not expect my respiratory problems to get any better | ☐ | ☐ |
| I have become frail or an invalid because of my respiratory problems | ☐ | ☐ |
| Exercise is not safe for me | ☐ | ☐ |
| Everything seems too much of an effort | ☐ | ☐ |

**Section 5**

***These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.***

| | For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True | False |
|---|---|---|
| My treatment does not help me very much | ☐ | ☐ |
| I get embarrassed using my medication in public | ☐ | ☐ |
| I have unpleasant side effects from my medication | ☐ | ☐ |
| My treatment interferes with my life a lot | ☐ | ☐ |

# Appendix B: St. George's Respiratory Questionnaire (SGRQ) (Continued)

## St. George's Respiratory Questionnaire

***Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):***

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....

.....

.....

.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

*Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.*

# Appendix C: University of California San Diego Shortness of Breath Questionnaire

UCSD Medical Center Pulmonary Rehabilitation
Program Shortness-of-Breath Questionnaire


Instructions: For each activity listed below, please rate your breathlessness on a scale between zero and five where 0 is not at all breathless and 5 is maximally breathless or too breathless to do the activity. If the activity is one which you do not perform, please give your best estimate of breathlessness. Your responses should be for an "average" day during the past week. Please respond to all items. Read the two examples below then turn the page to begin the questionnaire.

0 Not at all
1
2
3
4 Severely
5 Maximally or unable to do because of breathlessness

Example 1:
How short of breath do you get while:
1. Brushing teeth . . . 0 1 2 (3) 4 5
Harry has felt moderately short of breath during the past week while brushing his teeth and so circles a three for this activity.

Example 2:
How short of breath do you get while:
2. Mowing the lawn . . . 0 1 2 3 4 (5)
Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past week. She circles a five for this activity.

0 Not at all
1
2
3
4 Severely
5 Maximally or unable to do because of breathlessness

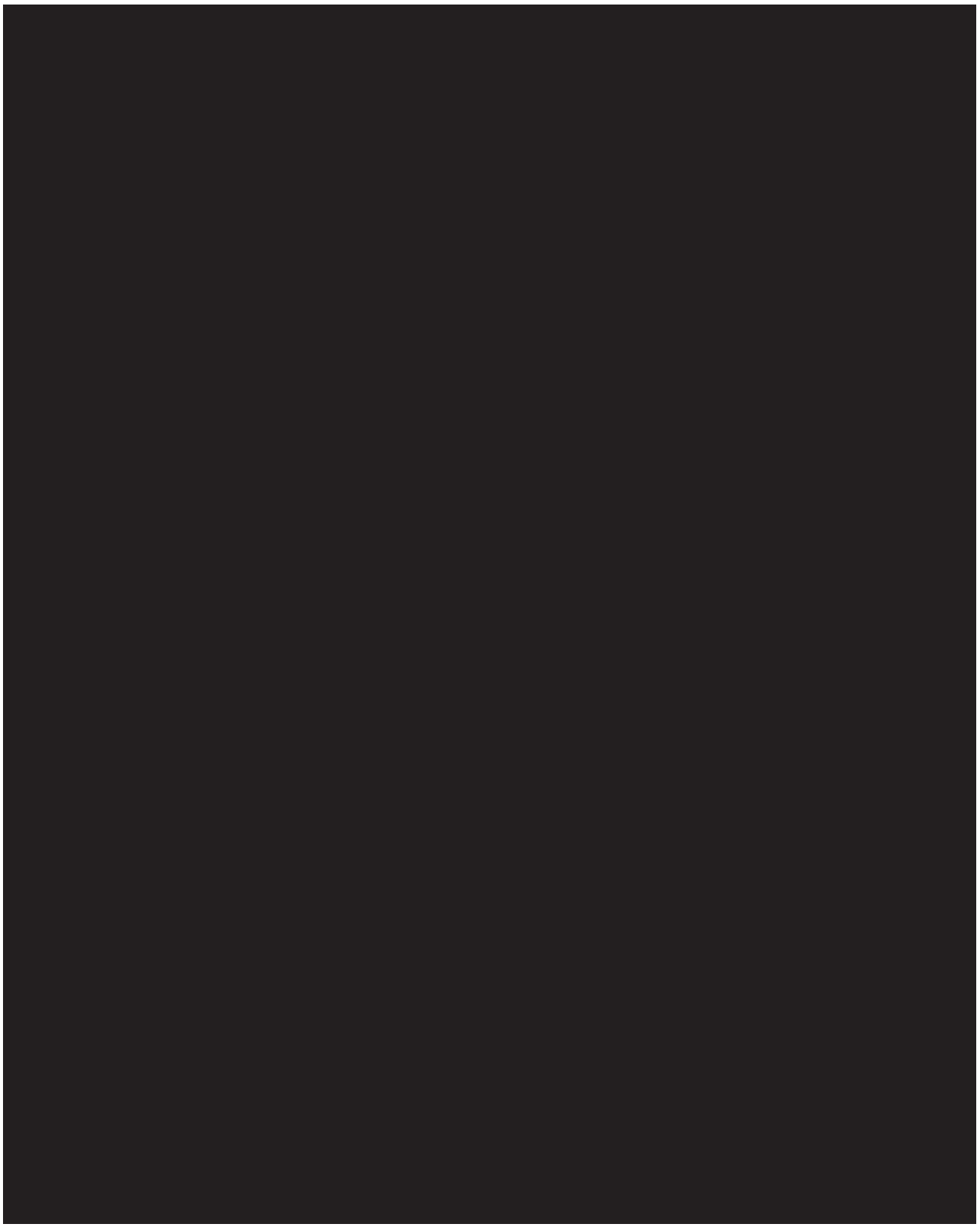
How short of breath do you get:

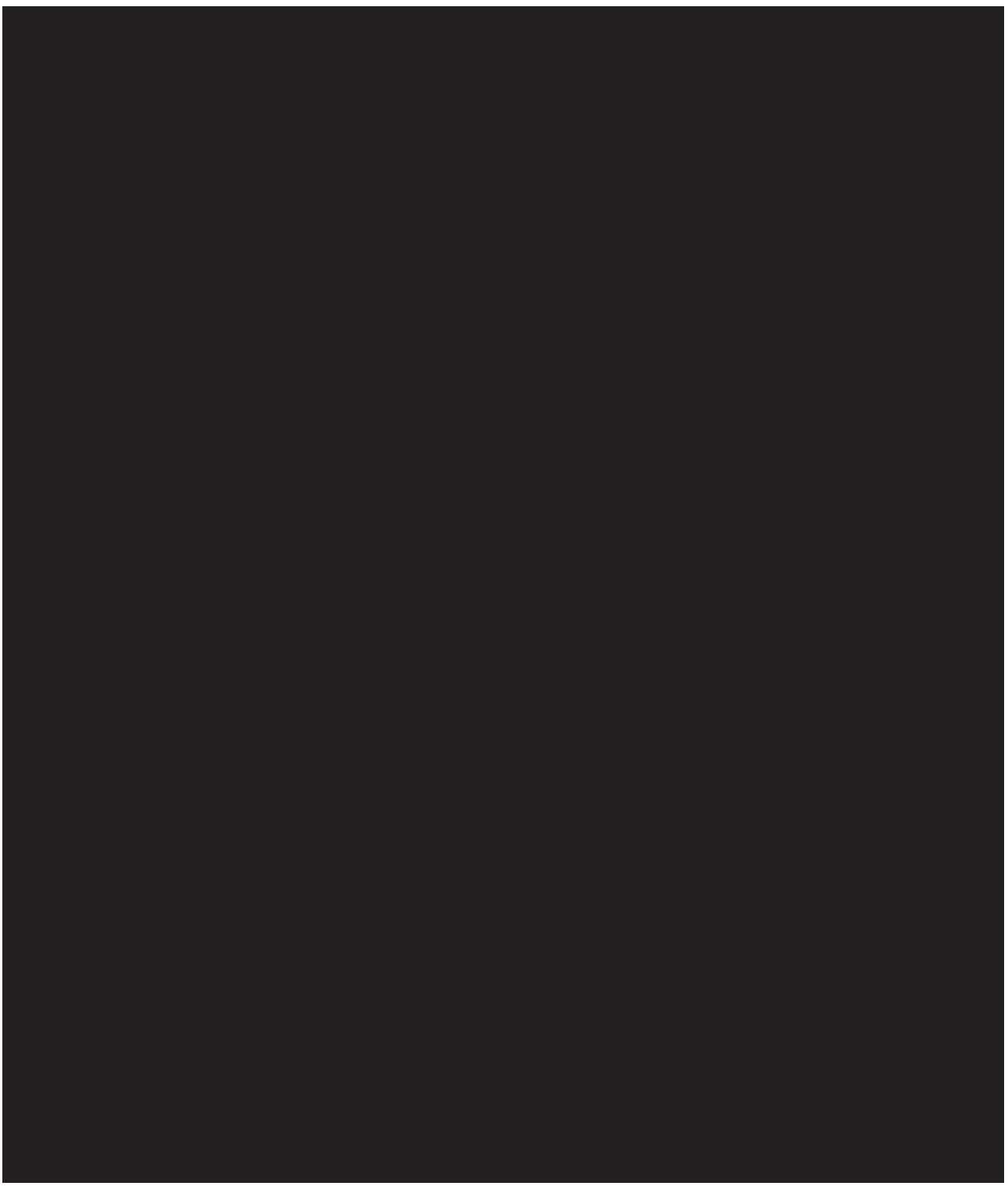
| | | | | | | |
|---|---|---|---|---|---|---|
| 1. At rest . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. Walking on a level at your own pace . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. Walking on a level with others your age . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Walking up a hill . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Walking up stairs . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. While eating . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. Standing up from a chair . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 8. Brushing teeth . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 9. Shaving and/or brushing hair . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 10. Showering/bathing . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 11. Dressing . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 12. Picking up and straightening . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 13. Doing dishes . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 14. Sweeping/vacuuming . . . | 0 | 1 | 2 | 3 | 4 | 5 |

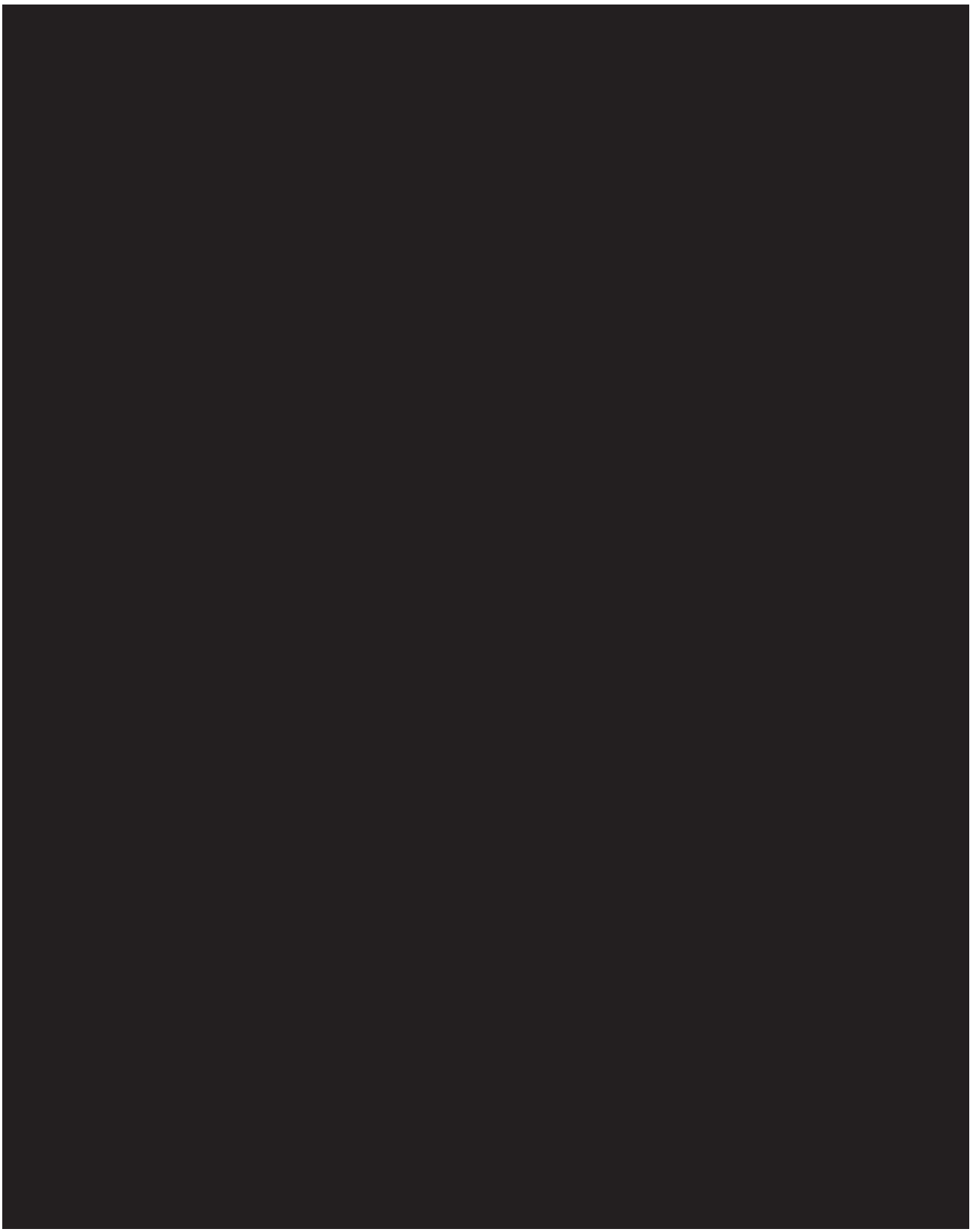
# Appendix C: University of California San Diego Shortness of Breath Questionnaire (Continued)

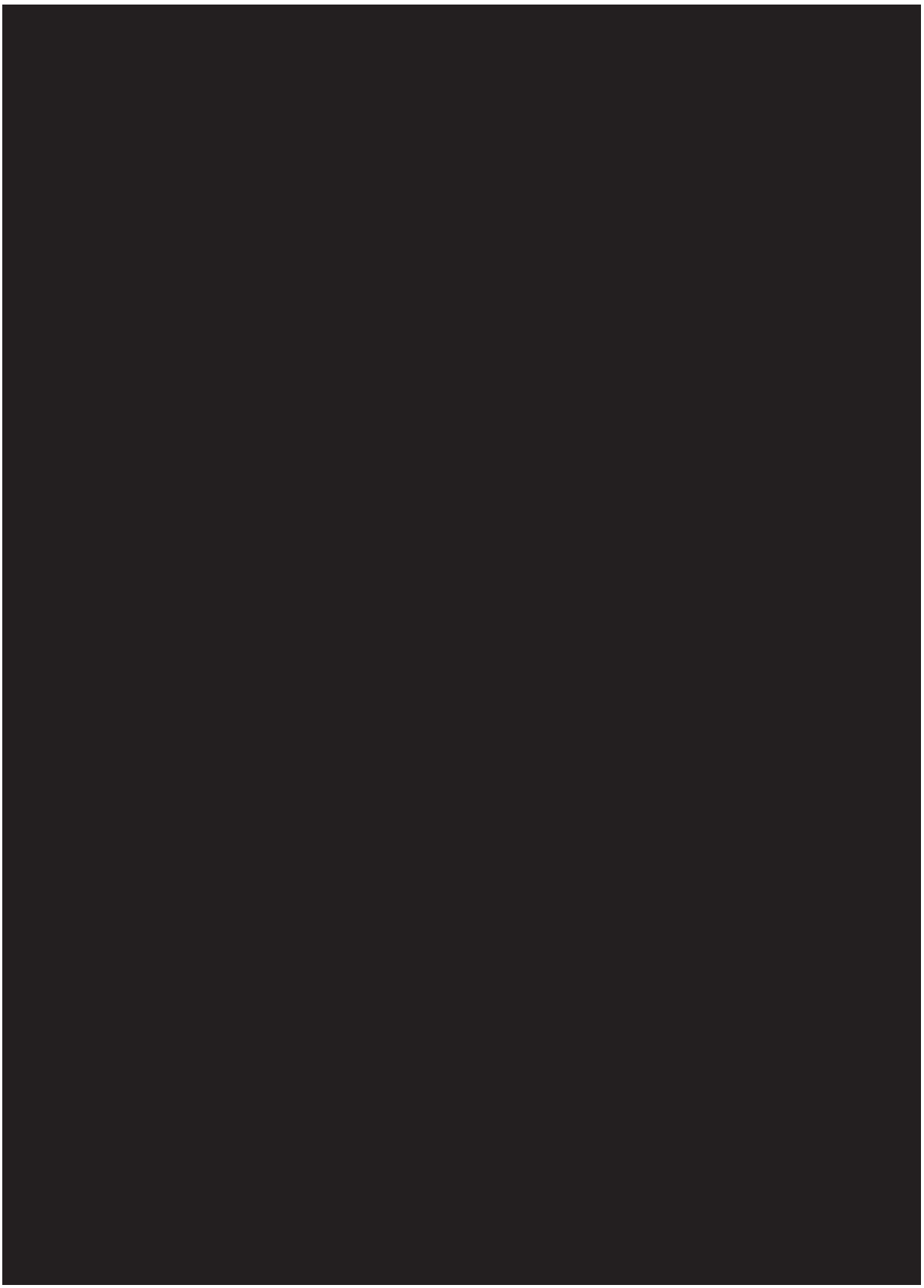
| | | | | | | |
|---|---|---|---|---|---|---|
| 15. Making bed . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 16. Shopping . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 17. Doing laundry . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 18. Washing car . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 19. Mowing lawn . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 20. Watering lawn . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 21. Sexual activities . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| How much do these limit you in your daily life? | | | | | | |
| 22. Shortness of breath . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 23. Fear of "hurting myself" by overexerting . . . | 0 | 1 | 2 | 3 | 4 | 5 |
| 24. Fear of shortness of breath . . . | 0 | 1 | 2 | 3 | 4 | 5 |

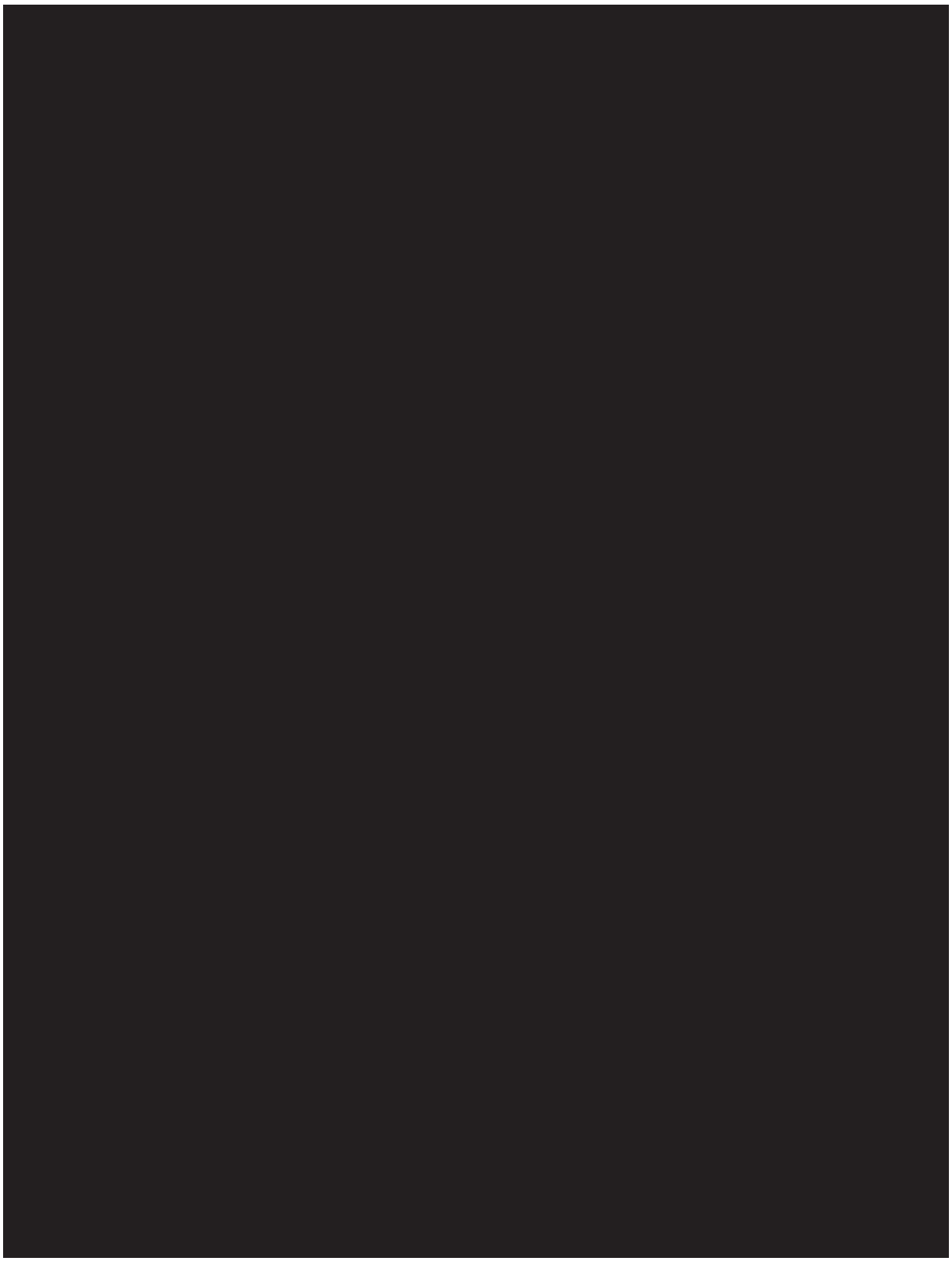
Eakin, 1998.

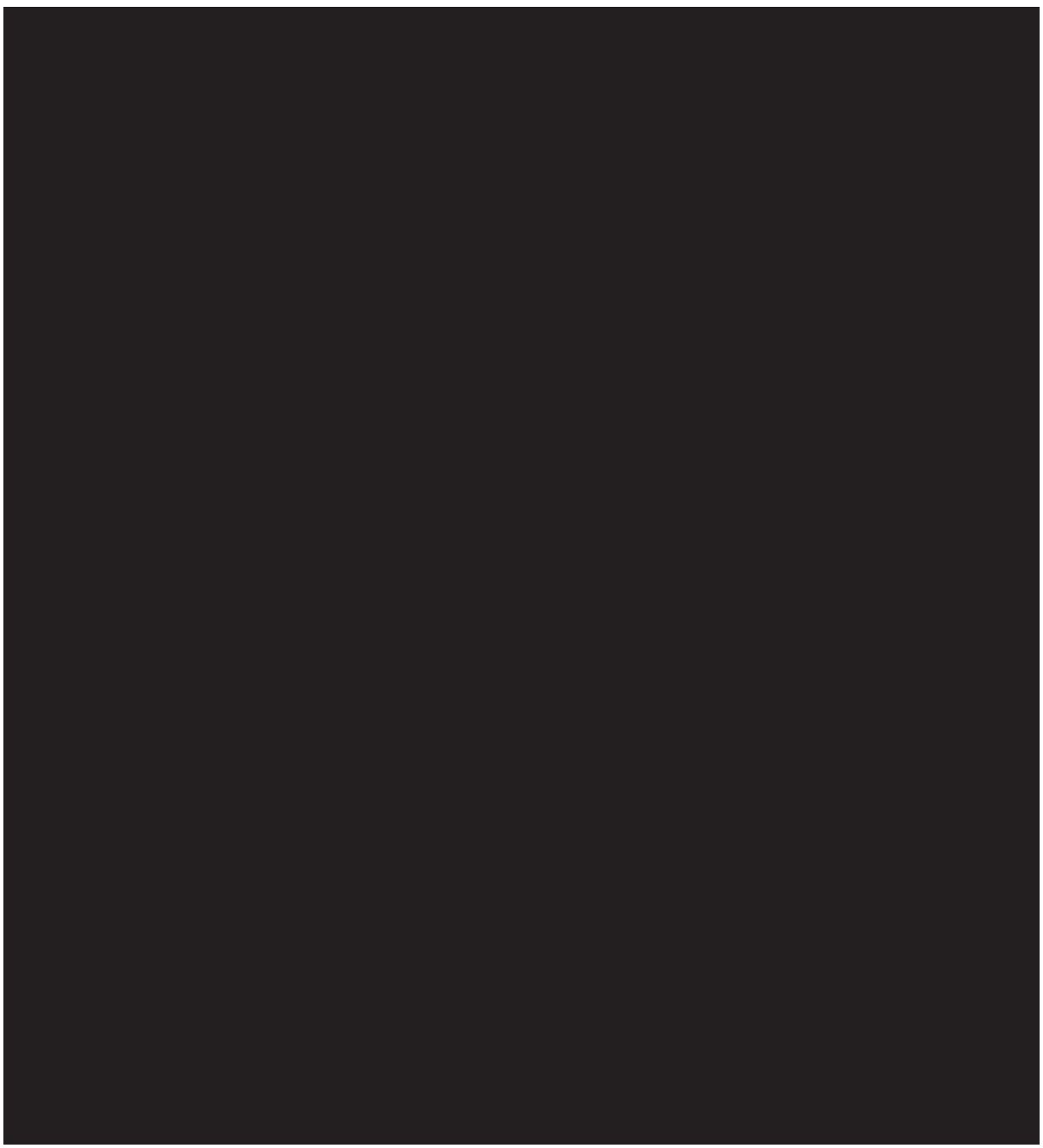












# Appendix E: 6-Minute Walk Test Protocol

The 6-minute walk test (6MWT) measures the distance that a patient can walk on a measured, flat hard surface in a period of 6 minutes. The objective is for patients to walk as far as possible during 6 minutes. The 6MWT evaluates the global and integrated responses of all body systems involved during walking. The instructions below incorporate the guidelines provided in the ATS statement for the 6MWT (ATS, 2002). It is imperative to follow the procedures in this document in order to ensure patient safety and control procedural sources of variability in the 6MWT.

## Location

The 6MWT should be performed indoors, along a flat, long, and straight corridor with a hard surface with little traffic. A process for controlling traffic that might interfere with the procedure should be in place. The walking course should be unobstructed, and between 20–40 meters in length, but as close to the standard of 30 meters (100 feet) as possible. The course should be marked with visible markers (eg, small traffic cones or chairs). A starting line, which marks the beginning and end of each approximately 60-meter lap, should be marked on the floor. The 6MWT course will be approved by the Sponsor during the qualification visit.

## Patient Safety

The walking test should be performed by trained personnel with experience and knowledge in exercise testing, basic cardiopulmonary resuscitation, $O_2$ therapy, blood pressure monitoring, and the application and limitations of pulse oximeters. Physicians are not required to be present during all tests. The primary Investigator (PI) will decide whether physician attendance is required. Patients with a history of unstable angina or myocardial infarction during the previous 6 months should not participate in a 6MWT. Blood pressure and pulse rate should be measured before the test. Relative contraindications to participation in the 6MWT include:

- Resting heart rate >120 beats per minute (bpm) or <60 bpm
- Systolic blood pressure >200 mm Hg or <80 mm Hg
- Diastolic blood pressure >110 mm Hg

Patients with any of these findings should be referred to the PI or designee, for clinical assessment and a decision about the conduct of the test. Supplies that must be available in proximity to the 6MWT course include $O_2$, sublingual nitroglycerine, aspirin and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help. The appropriate location of a crash cart should be determined by the PI.

## Appendix E: 6-Minute Walk Test Protocol (Continued)

Indications for immediate termination of the $O_2$ titration or the 6MWT procedure include the following (American Association for Respiratory Care, 1992; ATS, 2002):

- Angina
- Light headedness
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance
- Mental confusion or headache

The test administrators must be trained to recognize these problems and to respond appropriately should they occur. If a test is terminated for any of the above reasons, the patient should sit or lie supine as appropriate depending on the severity of the event, the test administrator's assessment of the severity of the event, and the risk of syncope. Once the patient is sitting or supine, blood pressure, pulse rate, and $O_2$ saturation should be obtained, and a physician evaluation performed.

**Personnel Performing the 6MWT**

It is essential that the personnel performing the 6MWT do not receive or solicit any information from the patient regarding adverse events or pulmonary symptoms. In order to minimize within-patient variability, if possible, the same person should perform the 6MWT for any given patient.

**Equipment**

The following equipment is used for the 6MWT:

- A stopwatch
- Mechanical lap counter
- Markers to identify the course
- Chair(s) or wheel chair that can be easily moved along the course
- Pad of worksheets on a clipboard
- Pulse oximeter
- Sphygmomanometer (blood pressure measurement device)
- Patient's usual $O_2$ supply and nasal cannula/tubing in addition to a back-up supply; back-up supply is preferably lightweight

# Appendix E: 6-Minute Walk Test Protocol (Continued)

- Measuring tape for precise determination of the distance walked
- Stethoscope

**Patient Preparation**

- Patients should wear comfortable clothing and shoes.
- In order to minimize intra-individual variability, the 6MWT should be performed as close to the same time of day as possible.
- A light meal is permitted before tests.
- The patient's usual medication regimen should be maintained the day of the walking test. If the patient routinely uses bronchodilators before a walk, then the patient should self-administer such bronchodilators 5–30 minutes before the 6MWT.
- A "warm-up" period before the test should not be performed.
- If the patient uses supplemental $O_2$, his/her delivery device and/or $O_2$ conserving system should be used if possible.

**Oxygen Titration Procedure (conducted only during the Screening Visit)**

At the time of the screening visit, the patient will undergo an $O_2$ titration procedure. The goal of the procedure is to objectively determine the necessary $O_2$ flow, up to and including 6 L/min, that the patient needs to complete the 6MWT without developing $O_2$ desaturation ($SpO_2$ <83%, where $SpO_2$ is $O_2$ saturation measured by pulse oximetry). This flow rate will represent the patient's baseline $O_2$ flow rate for the subsequent 6MWT procedures conducted at baseline and during the Study Period.

All increases in $O_2$ flow during the titration procedure will be in 2 L/min increments, such that all patients will start on 0 L/min, then sequentially increase to 2, 4, and then 6 L/min if necessary. This procedure includes a resting $O_2$ titration followed by a walking $O_2$ titration during the 6MWT. The $O_2$ flow rate determined during the walking $O_2$ titration procedure will be the $O_2$ flow rate that the patient receives for all subsequent 6MWT conducted during the study.

**STEP 1. Resting $O_2$ Titration**

A) The patient should be seated for at least 10 minutes, instructed to sit still and not to talk, and $O_2$ should be stopped. If the resting $SpO_2$ decreases to <83% in 5 minutes of rest off supplemental $O_2$, then start $O_2$ at 2 L/min. If following the initiation of $O_2$ at 2 L/min, the resting $SpO_2$ is <83% in 5 minutes, then increase $O_2$ to 4 L/min. If following the increase in $O_2$ to 4 L/min, the resting $SpO_2$ is <83% in 5 minutes, then increase $O_2$ to 6 L/min. If while on 6 L/min $O_2$, the resting $SpO_2$ is <83% in 5 minutes in Step 1, then the $O_2$ titration procedure should be terminated and the patient is not eligible for study participation.

# Appendix E: 6-Minute Walk Test Protocol (Continued)

B) The lowest flow for which a patient can maintain a resting SpO2 ≥83% for 5 minutes will be the initial flow rate in the walking portion (STEP 2) of the O2 titration procedure.

**STEP 2. Walking $O_2$ Titration**

A) Before starting the exercise evaluation, the patient should be seated and resting for at least 10 minutes on the flow rate determined during the resting $O_2$ titration procedure.

B) The test administrator should follow the actual 6MWT procedure (see below) during the walking $O_2$ titration for each level of $O_2$ flow evaluated.

C) After the patient begins walking, if the patient's $SpO_2$ decreases to below 83% at any time:

- The walk should be terminated,
- The patient's $O_2$ flow should be increased by 2 L/min,
- The patient should then be seated and allowed to rest for 5 minutes.
- If the resting $SpO_2$ after 5 minutes is not ≥ 83%, then the $O_2$ flow rate should be increased another 2 L/min and the resting $SpO_2$ reassessed after 5 minutes. This should be repeated until the resting $SpO_2$ is ≥ 83% for 5 minutes.

D) The walking $O_2$ titration procedure should then be repeated at the higher $O_2$ flow rate. If the patient's $SpO_2$ decreases to below 83% at any time, Steps 2C and 2D will be repeated.

E) If a patient is titrated during the walking $O_2$ titration to 6 L/min of $O_2$, and within 6 minutes of the 6MWT on 6 L/min of $O_2$ the $SpO_2$ drops below 83%, then the Walking $O_2$ titration should be terminated and the patient is not eligible for study participation.

F) The lowest flow on which a patient can complete the 6MWT without developing a $SpO_2$ < 83% will be the patient's $O_2$ flow for all subsequent 6MWT conducted during the course of the study.

**6MWT Procedure:**

1. The 6MWT will be performed during the oxygen titration procedure at screening, on the day of randomization, and every 24 weeks during the study.
2. Seat the patient in a chair near the starting line, deliver the baseline $O_2$ flow rate determined during the oxygen titration procedure at the screening visit, apply pulse oximetry probe, and have the patient rest for at least 10 minutes. If the patient's resting $SpO_2$ after 10 minutes of rest on the baseline $O_2$ flow rate is <83%, then the patient should not participate in the 6MWT. Ensure patient's vital signs are in compliance with the guidelines in patient safety section.

## Appendix E: 6-Minute Walk Test Protocol (Continued)

3. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the markers. You should turn briskly around the markers and continue back the other way without hesitation. Now, I'm going to show you so please watch the way I turn without hesitation." The walk administrator should demonstrate by walking one lap. "Are you ready to do that? I am going to use this counter to keep track of the number of times you complete a lap. Remember that the object is to walk as far as possible for 6 minutes, but don't run or jog. I am going to walk behind you and watch your oxygen saturation. When I say stop, I want you to stop walking and stand where you are. I will bring you a chair if you need to sit down."

4. Have the patient stand and use the Borg scale (see below) before walking to measure perceived dyspnea and record $SpO_2$ and pulse rate (from pulse oximeter).

5. The patient, and not the test administrator, should carry and/or pull his/her $O_2$ delivery device and/or conserving system, as they do in everyday life. The patient should use his/her own $O_2$ delivery device and/or conserving system whenever possible. If the patient does not have his/her own equipment, attempts should be made to use equipment the patient is familiar with and to use the lightest weight equipment possible. Patients should use the same equipment during all 6MWTs performed during the Study Period. The test administrator will carry and monitor the pulse oximeter.

6. Position the patient at the starting line.

7. As soon as the patient starts to walk, start the timer. The test administrator should walk behind the patient to monitor the pulse oximeter and should not influence the pace. The test administrator should monitor for the lowest $SpO_2$ measured during the 6-minute time interval following the start of the walk and this value will be recorded on the CRF.

8. During the walk test, the administrator should not talk to anyone else except the patient. Use an even tone of voice when using the following standard phrases of encouragement. The test administrator should watch the patient and not get distracted.

9. It is important that only the following standard phrases of encouragement be used for all the 6MWTs:

   - After the first minute: "You are doing well. You have 5 min to go."
   - After the 2nd minute: "Keep up the good work. You have 4 min to go."
   - After the 3rd minute: "You are doing well. You are halfway done."
   - After the 4$^{th}$ minute: "Keep up the good work. You have only 2 min left."

## Appendix E: 6-Minute Walk Test Protocol (Continued)

- After the 5th minute: "You are doing well. You have only 1 min to go."
- With 15 seconds to go: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

10. The test should terminate when any of the following occur:
    - Six minutes are up
    - $SpO_2$ is <83%
    - Patient develops signs or symptoms requiring test termination (see above patient safety section)

At the time of termination, the test administrator should say "Stop!", and mark the spot they stopped by placing a bean bag or piece of tape on the floor. If the test is terminated for reasons other than the completion of 6 minutes of walking, the guidelines outlined above in the patient safety section should be followed.

11. The test administrator should record the post-walk dyspnea score using the Borg scale immediately following the completion of the 6MWT, and the lowest $SpO_2$ observed during the 6MWT.
12. The number of laps traveled and the additional distance covered (number of meters in the final partial lap) should be recorded.
13. The test administrator should calculate the total distance walked in meters, rounding to the nearest meter.
14. The test administrator should congratulate the patient on good effort, and offer a drink of water.

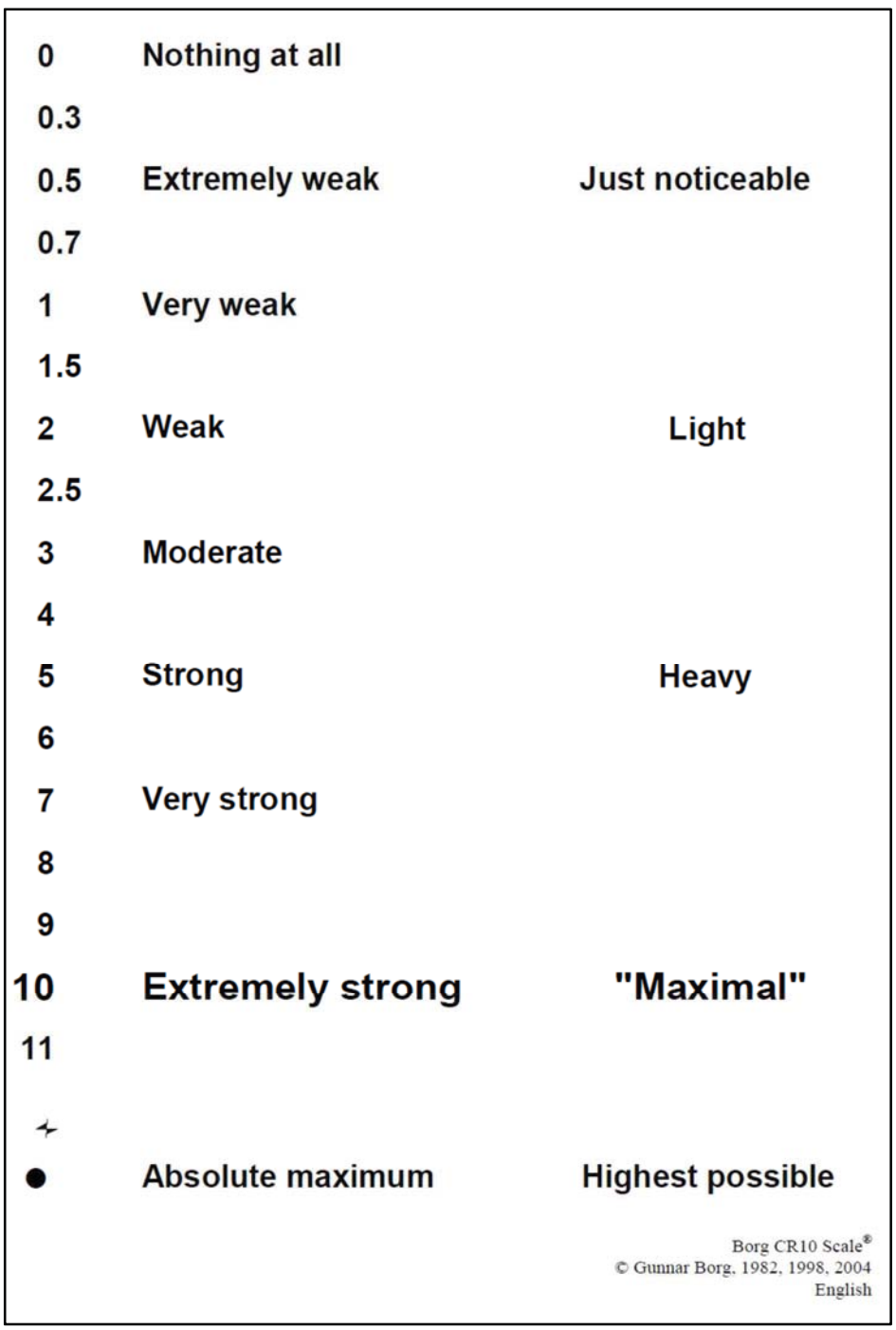
**NOTE:** If the patient stops during the test and needs to rest, they should be told, "You can lean against the wall if you would like; then continue walking whenever you feel you are able."

The timer should continue to run. If the patient stops before the 6 minutes are up and does not wish to continue, or the test administrator determines that they should not continue, a chair should be taken to the patient to sit on. The reason the 6MWT was terminated, the time of termination, and the distance walked at termination should be recorded in all cases.

**References**

American Association for Respiratory Care, 1992; ATS, 2002.

## Appendix F: Borg Scale



# Appendix G: Diagnostic Categories of UIP Based on HRCT Patterns and Histopathological Criteria For UIP in IPF

## A. Diagnostic Categories of UIP Based on HRCT Patterns

| | Typical UIP HRCT pattern | Probable UIP HRCT pattern | HRCT pattern indeterminate for UIP | HRCT features most consistent with non-IPF diagnosis |
|---|---|---|---|---|
| **Distribution** | Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous | Basal and subpleural predominant;<br>distribution is often heterogeneous | Variable or diffuse | Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing |
| **Features** | Honeycombing; reticular pattern usually associated with peripheral traction bronchiectasis or bronchiolectasis[a]; absence of features to suggest an alternative diagnosis | Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis[a]; honeycombing is absent; absence of features to suggest an alternative diagnosis | Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern | Any of the following:<br>predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts |

Abbreviations: HRCT=high resolution computed tomography; IPF=idiopathic pulmonary fibrosis; UIP=usual interstitial pneumonia.

[a] Reticular pattern is superimposed on ground glass opacity, and in these cases, it is usually fibrotic. Pure ground glass opacity, however, would be against the diagnosis of UIP or IPF and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions.

Adapted from Lynch, 2018.

# Appendix G: Diagnostic Categories of UIP Based on HRCT Patterns and Histopathological Criteria For UIP in IPF (Continued)

## B. Histopathological Criteria for UIP in IPF (UIP-IPF)

| | Definite UIP-IPF | Probable UIP-IPF | Indeterminate for UIP-IPF | Features most consistent with an alternative diagnosis |
|---|---|---|---|---|
| **General comments** | Patients show features with all four criteria, and do not show features that might suggest an alternative diagnosis (eg, non-UIP) | Patients show either honeycomb fibrosis only, or a severe fibrosing process that falls short of showing all four criteria for definite UIP-IPF and do not show features that might suggest an alternative diagnosis | Patients show evidence of a fibrosing process but with features that are more in favor of either a non-UIP pattern, or UIP in a setting other than IPF | Patients show either a UIP pattern with ancillary features strongly suggesting an alternative diagnosis, or a non-UIP pattern (see cell below) |
| **Specific criteria** | Dense fibrosis causing architecture remodeling with frequent honeycombing; patchy lung involvement by fibrosis; subpleural or paraseptal distribution, or both; fibroblast foci at the edge of dense scars | Honeycomb fibrosis only or; dense fibrosis causing architecture remodeling with frequent honeycombing; patchy lung involvement by fibrosis; fibroblast foci at the edge of dense scars may or may not be present | Patients have less compelling histological changes than those classified by the final column (eg, occasional foci of centrilobular injury or scarring, rare granulomas or giant cells, only a minor degree of lymphoid hyperplasia or diffuse inflammation, or diffuse homogenous fibrosis favoring fibrotic non-specific interstitial pneumonia); these features, and the differential diagnoses they call to mind, become part of the multidisciplinary discussion and decision with regard to a multidisciplinary diagnosis of IPF, or not | Non-UIP pattern: patients with features of other fibrotic disorders, eg, fibrotic hypersensitivity pneumonitis, fibrotic non-specific interstitial pneumonia, fibrosing organizing pneumonia, pleuroparenchymal fibroelastosis, pulmonary Langerhans cell histiocytosis, or smoking-related interstitial fibrosis; UIP pattern with ancillary features strongly suggesting an alternative diagnosis: eg, prominent diffuse alveolar damage or organizing pneumonia (consider acute exacerbation of UIP), granulomas, (consider hypersensitivity pneumonitis, sarcoid, infection), marked interstitial inflammatory cell infiltrate away from areas of UIP (consider hypersensitivity pneumonitis) |

Abbreviations: HRCT=high resolution computed tomography; IPF=idiopathic pulmonary fibrosis; UIP=usual interstitial pneumonia.
Adapted from Lynch, 2018.

# Appendix H: Examples Of Drugs That Are Substrates For Selected Transporters

**Examples of In Vivo Substrates for Selected Transporters**

| Transporter | Gene | Substrate |
|---|---|---|
| P-gp | *ABCB1* | aliskiren, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan |
| OATP1B1 | *SLCO1B1* | atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, valsartan, olmesartan |
| OATP1B3 | *SLCO1B3* | atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan |
| BCRP | *ABCG2* | rosuvastatin, sulfasalazine |

Abbreviations: BCRP = ATP binding cassette protein G2/ABCG2; OAT1B1 = organic anion transporting polypeptide 1B1; OAT1B3 = organic anion transporting polypeptide 1B3; P-gp = p-glycoprotein.

**Examples of Substrates of One or More Transporters with a Narrow Therapeutic Index**

| Substrate |
|---|
| digoxin |
| mycophenolate mofetil |
| procainamide |

# Celgene Signing Page

**This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.**

UserName: [redacted]
Title: [redacted]
Date: Thursday, 29 August 2019, 01:04 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

# 1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this amendment is to allow subjects with idiopathic pulmonary fibrosis (IPF) receiving protocol-allowable standard of care (SOC) treatment to be enrolled in the study. Consequently, the number of subjects planned for enrollment was increased from 135 to 165 to obtain an adequate number of subjects receiving SOC.

[redacted]

[redacted]

Significant changes included in this amendment are summarized below:

- **Inclusion of subjects with IPF receiving protocol-allowable standard of care (SOC) treatment**

  This change was instituted to determine whether subjects already receiving SOC demonstrate a treatment benefit from CC-90001, as compared to placebo. The number of randomized IPF subjects was increased from 135 to 165 to allow for an adequate estimation of efficacy, safety and tolerability in subjects receiving SOC. [redacted]

  [redacted]

  – Protocol Summary (Study Design and Statistical Methods);

  [redacted]

  – Section 1.6.2 (Rationale for the Study Design) – was originally Section 1.7.2;

  – Section 1.6.5 (Rationale for Placebo Comparator) – was originally Section 1.7.5;

  – Section 3.1 (Study Design and Figure 1: Overall Study Design [Idiopathic Pulmonary Fibrosis Study]);

  – Section 4.1 (Number of Subjects);

  [redacted]

  – Section 7.2 (Treatment Administration and Schedule);

[redacted]

- Section 8.4 (Required Concomitant Medications);
- Section 9.3 (Sample Size and Power Considerations);
- Section 9.6.1 (Analysis of the Primary Efficacy Endpoint for the IPF Study);
- Section 9.6.2.1 (24-Week Double-blind Placebo-controlled Treatment Phase);
- Section 9.8 (Interim Analysis)

- **Exploratory PPF Substudy**

  A separate, exploratory substudy in subjects with PPF will be initiated after a decision allows continuation of the IPF study as planned from an interim analysis. Subjects who were initially screened for the IPF study and did not meet eligibility based on the central reader criteria for IPF based on high resolution computed tomography (HRCT) and lung biopsy, if provided, but met the PPF inclusion criteria will be considered for the PPF substudy. The rationale for studying these subjects is that they may also benefit from anti-fibrotic treatments, such as CC-90001. Approximately 45 qualifying non-SOC PPF subjects will be enrolled into the substudy.

  - Revised or newly added content in the following sections based on the inclusion of the PPF substudy:
    - Protocol Summary (Secondary Objectives, [redacted] Study Design, Study Treatments and Statistical Methods);
    - Section 1.1.2 (Progressive Forms of Pulmonary Fibrosis Other Than IPF) – a newly added section;

[redacted]

    - Section 2 (Study Objectives and Endpoints) – Secondary Objectives [redacted] related to the PPF substudy were added to Table 1;

- Section 2 (Study Objectives and Endpoints) – Table 3 (Progressive Pulmonary Fibrosis Substudy Endpoints) was added;
- Section 3 (Overall Study Design) with newly added Figure 2 (Overall Study Design [Progressive Pulmonary Fibrosis Substudy]);
- Section 3.1 (Study Design);
- Section 3.1.1 (Progressive Pulmonary Fibrosis Substudy) – newly added section;
- Section 4.1 (Number of Subjects);
- Section 4.2.2 (Inclusion Criteria for Progressive Pulmonary Fibrosis Substudy Only) – newly added section;
- Section 4.3 (Exclusion Criteria) – Some of the wording was updated so that it applies to both IPF and PPF populations. Also, Exclusion Criterion No. 9 has a newly added "Note" that only applies to the PPF population;
- Section 6.1 (Screening Phase);
- Section 7.2 (Treatment Administration and Schedule);
- Section 9.1 (Overview);
- Section 9.2 (Study Population Definitions);
- Section 9.3 (Sample Size and Power Considerations);
- Section 9.6.1 (Analysis of the Primary Efficacy Endpoint for the IPF Study);
- Section 9.6.2.1 (24-Week Double-blind Placebo-controlled Treatment Phase);
- Section 9.8 (Interim Analysis)

- **Inclusion Criteria Revised**

  Section 4.2 (Inclusion Criteria) was updated to include two sub-sections, Sections 4.2.1 and 4.2.2, as described below.

  - Section 4.2.1 (Inclusion Criteria for Idiopathic Pulmonary Fibrosis Subjects) was added as a subsection for IPF subjects.
    - Inclusion Criterion No. 5 (original) – was deleted to allow subjects with a prior IPF diagnosis longer than 5 years to be considered for participation in the study. Some patients with IPF have a more protracted course of disease [redacted] and there is no reason to suspect that CC-90001 would not be potentially beneficial in these patients.
    - Inclusion Criterion No. 12 (originally Inclusion Criterion No. 13) – was revised with updated program-wide female contraception language, based on the latest updated Celgene template.
    - Inclusion Criterion No. 13 (originally Inclusion Criterion No. 14) – was revised with updated program-wide male contraception language, based on the latest updated Celgene template.

- Section 4.2.2 (Inclusion Criteria for Progressive Pulmonary Fibrosis Substudy Only) was added as a subsection for PPF subjects.

- **Exclusion Criteria Revised**
  - Section 4.3 (Exclusion Criteria)

    [redacted]

    - Exclusion Criterion No. 22 – was revised to account for allowing subjects with documentation of adequately treated latent or active tuberculosis (TB) to participate in the study. Also, a "Note" was added to this Criterion and Section 6.1 (Screening) to describe when the QuantiFERON-TB Gold test is not required for adequately treated subjects, provided there is a chest radiograph taken prior to or during Screening to rule out latent/active TB and there is documentation of adequate treatment for TB prior to randomization.
    - Exclusion Criterion No. 23 (newly added) – was added for excluding subjects who had household contact with a person with active TB and the subject did not receive appropriate and documented prophylaxis for TB.

- **Dose Interruptions for Planned Surgical Procedures**

  Section 7.2.2.1 (Dose Interruptions for Planned Surgical Procedures) was added to emphasize that subjects with planned surgical procedures should interrupt investigational product (IP) 7 to 10 days prior to and restart 7 days after any surgical procedures, since it is unknown if CC-90001 affects wound healing in humans.

- **Changes to Statistical Sections**

  The study is no longer powered at 80% since the proposed IPF patient population will include both non-SOC and SOC IPF subjects and benefits of CC-90001 in subjects already receiving anti-fibrotic therapy are expected to be reduced. The inclusion of a PPF substudy population will be analyzed as a separate population. Additional supportive analyses (eg, efficacy analysis of both active treatment groups, considered together, versus placebo, and a Bayesian approach to efficacy analysis) are specified.

  - Revised content in the following sections based on the changes to the statistical section:
    - Protocol Summary (Study Design and Statistical Methods);
    - The original Section 1.6 (Study Hypothesis) was removed since it no longer applies, and the purpose of the study is to estimate the effect of CC-90001 in IPF subjects either not receiving SOC or currently receiving SOC. As a result, sections previously labeled as 1.7, 1.7.1, 1.7.2, 1.7.3, etc, are re-numbered accordingly.
    - Section 9.2 (Study Population Definitions);
    - Section 9.3 (Sample Size and Power Considerations);
    - Section 9.6.1 (Analysis of the Primary Efficacy Endpoint for the IPF Study);
    - Section 9.6.2.1 (24-Week Double-blind Placebo-controlled Treatment Phase);

- Section 9.8 (Interim Analysis);
- Section 9.9.3 (Analysis of Dose-Response) – was newly added to briefly describe the analysis approach used to inform optimal dose selection.

**This amendment also includes other administrative, corrective and/or minor changes, which are summarized below:**

- In multiple sections throughout the amendment, the term "Placebo-controlled" was appropriately added to previous phrase, "24-week Double-blind Treatment Phase," to emphasize that the first 24 weeks of the study are placebo-controlled. "24-week Double-blind Placebo-controlled Treatment Phase" is now consistently stated throughout the protocol.
- In Protocol Summary (Study Design, Length of Study and Study Treatments), Section 3.1 (Study Design), Section 3.2 (Study Duration for Subjects), and Section 7.2 (Treatment Administration and Schedule), detailed descriptions regarding Protocol Amendments 1.0 and 2.0 that no longer apply were deleted.

- Section 1.7 (Potential Risks of CC-90001 and the Study Population) which was previously Section 1.7.8, and Section 8.1.1 (Permitted Concomitant Medications Throughout the Entire Study) were revised with minor word changes for a better description regarding concomitant statins, which will be dose adjusted to a therapeutic level during the study.
- Sections 2 and 3 (Study Objectives and Endpoints and Overall Study Design) had Table 2 and Figure 1 titles relabeled to specifically define the endpoints in Table 2 as the "Idiopathic Pulmonary Fibrosis Study Endpoints" and Figure 1 as the Overall Study Design "Idiopathic Pulmonary Fibrosis Study," since a separate Table 3 and Figure 2 were added to define the "Progressive Pulmonary Fibrosis Substudy Endpoints" and Overall Study Design "Progressive Pulmonary Fibrosis Substudy," respectively. Also, Table 2 (Idiopathic Pulmonary Fibrosis Study Endpoints) has been updated with additional timeframes for analysis of endpoints.
- Section 3.1.2 (Adjudication Committee), which was previously Section 3.1.1, and Protocol Summary (Adjudication Committee) were slightly revised to include the same content and minor word changes for a better description of the content within both sections.

- Section 4.2 (Inclusion Criteria, newly labelled as Inclusion Criterion No. 5), Section 5 (Table of Events, Table 5, which was previously Table 4) Footnote "e", Section 6.1 (Screening Phase), and Section 6.4.5 (Chest High-resolution Computed Tomography) were slightly revised for a clearer description regarding eligible historical HRCT scans. The wording "if it meets image acquisition guidelines and scan is reviewed by" centralized review was changed to "if the scan is deemed sufficient for" centralized review in the following paragraph:
  *HRCT scan performed within 18 months of randomization may be used if it meets image acquisition guidelines and scan is reviewed by centralized review. For sites subject to regulatory restrictions that do not permit HRCT within this time period, a previous HRCT scan is permissible "if the scan is deemed sufficient for" centralized review.*

- Section 5 (Table of Events, Table 5, which was previously Table 4) Footnote "h" was revised to remove the erroneous letter "E" after Weeks 12, 16, 20, and 24.
- Section 5 (Table of Events, Table 5, which was previously Table 4) has a newly added Footnote "k" and Section 6.2 (Treatment Phase) and Section 6.3 (Post-treatment Observational Follow-up Phase) were revised to better describe the scheduling of visits. For all subsequent visits, an administrative window of ± 3 days is permitted. Scheduling of Visits 3 to 9 is based on Visit 2 (randomization date) and scheduling of Visits 10E to 26E is based on Visit 9 (re-randomization date). The Post-treatment Observational Follow-up Visit is scheduled 28 days (4 weeks) after the date of the last dose of IP ± 3 days.
- Section 5 (Table of Events, Table 5, which was previously Table 4) has a newly added Footnote "l" and Section 6.1 (Screening Phase) was updated with a new "Note" to describe when the QuantiFERON-TB Gold test is not required for a subject, provided there is a chest radiograph taken prior to or during Screening to rule out latent/active TB, and documentation of adequate treatment for TB prior to randomization.
  Also, within Table 5 (Table of Events), the QuantiFERON® -TB Gold Test, Hepatitis B & C Tests assessment row was updated to include "or Chest Radiograph for TB when appropriate."
- Section 6.1 (Screening Phase) was revised with corrections in the following 2 sentences:
  - A correction to note that screening evaluations must be completed within 8 weeks "after Screening (Visit 1)" and not within 8 weeks "of Baseline (Visit 2)."

  - A correction to note that if the subject does not receive IP within 8 weeks "after Screening (Visit 1)," the subject must be screen failed. Previously, it was stated as "if the subject does not receive IP within 8 weeks of Baseline (Visit 2)" which was incorrect.

- Section 6.1 (Screening Phase), first paragraph, last sentence was revised with an additional statement to emphasize that all re-screened subjects must be re-consented for the study.
- For Section 6.1 (Screening Phase), the following new "Note" was added to emphasize to the site to perform a urine culture test, if the Screening Visit 1 urinalysis test results are positive for leukocyte esterase or nitrite present:
  *Note: If the Screening Visit 1 urinalysis test results are positive (eg, leukocyte esterase or nitrite present), a urine culture test is required, and the subject must have a confirmatory negative urine culture test to rule out urinary tract infection (UTI) prior to randomization, which can be performed using the provided central laboratory urine culture kits or a local laboratory at the site.*
- For Section 6.3 (Post-treatment Observational Follow-up Phase), the order of the assessments for concomitant medications and concomitant procedures were adjusted to match the order in Section 6.2 (Treatment Phase) for consistency.
- The IP sections, Section 7.2 (Treatment Administration and Schedule) and Protocol Summary (Study Design and Study Treatments) were updated with summarized information to better describe the IP treatments and the number and type of tablets taken by subjects during the 24-week Double-blind, Placebo-controlled Treatment Phase versus the 80-week Active Treatment Extension Phase. Also, a clear description of when the IP is taken during each phase was provided in Section 7.2.

[redacted]

- Section 9.7.2 (Disease Progression) was revised to clarify that the Investigator's discretion to discontinue the subject can also apply if the subject experiences a decrease from baseline of ≥ 50 meters in 6-minute Walk Test (6MWT) distance (in the absence of a readily explainable cause, such as injury or trauma).
- In Section 9.8 (Interim Analysis), Section 9.9.4 (External Data Monitoring Committee) and Protocol Summary (External Data Monitoring Committee), content was added to describe the Data Monitoring Committee's (DMC's) role and responsibility in reviewing the interim analyses data. The DMC will make recommendations to a Celgene Internal Review Committee, who will remain independent from the Study Team, and will be responsible for final decision making.
- Section 10.4 (Pregnancy) was updated with language regarding the new process for Celgene to obtain consent for collecting pregnancy information from a female subject of childbearing potential, or female partner of a male subject, in the event that a

pregnancy occurs during the study, which requires the release of the new Celgene pregnancy-specific information consent forms.

- Section 17 (References) was updated with additonal citations based on newly added content.
- Section 18 (Appendix E. 6-Minute Walk Test Protocol) was updated with a correction in the instructions for Step 2: Walking $O_2$ Titration Procedure, bullet E. The Walking $O_2$ titration should be terminated and the patient deemed not eligible for study participation if a patient is titrated during the walking $O_2$ titration to 6 L/min of $O_2$ and within the "6 minutes" of the 6MWT the oxygen saturation ($SpO_2$) drops below 83%.
- Other minor editorial changes were made throughout the document.

# 1. JUSTIFICATION FOR AMENDMENT

The rationale for the following changes is to allow idiopathic pulmonary fibrosis (IPF) subjects who were randomized to placebo the opportunity to receive CC-90001 (200 mg or 400 mg orally [PO] once a day [QD]) after 24 weeks of treatment. In the current study design, these subjects are not given the opportunity to receive CC-90001. It will also afford all subjects to receive active treatment for an additional 52 weeks (80-week Active Treatment Extension Phase).

Significant changes included in this amendment are summarized below:

- **Protocol Title (Title Page and Protocol Summary)**

  The title was changed to: "A Phase 2, 24-Week, Randomized, Double-blind, Placebo-controlled, Multicenter Study, With an 80-Week Active Treatment Extension, to Evaluate the Efficacy and Safety of CC-90001 in Subjects With Idiopathic Pulmonary Fibrosis."

- **Study Design (Protocol Summary and Section 3.1)**

  The study design was changed to include an 80-week Active Treatment Extension Phase. The 80-week Active Treatment Extension Phase will provide subjects who were randomized to placebo the opportunity to receive CC-90001 (200 mg or 400 mg PO QD) after completing Week 24 of the study.

  – Added a description of how subjects who were enrolled under the original protocol and Protocol Amendment 1.0 will continue in the study under Protocol Amendment 2.0 and may receive treatment for up to 132 weeks.

  – The length of the study was revised to 116 weeks; 8-week Screening Phase, 24-week Double-blind Placebo-controlled Treatment Phase, 80-week Active Treatment Extension Phase and 4-week Post-treatment Observational Follow-up Phase.

  – Added text that describes the randomization of subjects stratified by previous exposure to pirfenidone, nintedanib or no prior exposure to either drug.

- **Study Duration and Length of Study (Protocol Summary, Figure 1, and Section 3.2)**

  – The study figure was revised to reflect an 80-week Active Treatment Extension Phase.

  – The study duration was revised based upon the 80-week Active Treatment Extension Phase to include a total duration of up to 116 weeks for those subjects enrolled under Protocol Amendment 2.0.

  – Clarified that subjects enrolled under the original protocol or under Protocol Amendment 1.0 can have a total study duration of up to 141 weeks.

  – Screening Phase: The Screening Phase was revised to permit screening for up to 8 weeks.

The 8-week screening will prevent subjects from falling out of the screening window due to scheduling conflicts within institutions' radiology (high resolution computerized tomography [HRCT]) and pulmonary departments (spirometry and diffusion capacity of the lung for carbon monoxide [$D_LCO$]).

- **Study Endpoints (Section 2, Table 2)**
  - Revised the timeframe for several endpoints described in Table 2.

    Due to the change in the study design, the timeframe for several study endpoints needed to be adjusted.
- **Inclusion Criteria (Section 4.2)**
  - Revised inclusion criterion number 5 regarding years since the diagnosis of IPF at screening from within 4 years to within 5 years.

    The median survival rate for IPF is 3 to 5 years from the time of diagnosis (Ley, 2013). Therefore, the inclusion of patients with a history of IPF within 5 years is still representative of the general population of IPF patients. More recent IPF trials (eg, pirfenidone [King, 2014], nintedanib [Richeldi, 2014], pamrevlumab [NCT01890265] and KD025 [NCT02688647]) have included a 5-year window from the time of diagnosis for study eligibility.
  - Revised inclusion criterion number 6 and Section 6.1 regarding the diagnosis of IPF. Appendix G and Table 3 that is referenced in inclusion criterion number 6 were also revised.

Criteria to establish the diagnosis of IPF have continued to evolve since publication of the ATS/ERS/JRS/ALAT statement in 2011. It has become increasingly recognized that the absence of honeycombing has a poor negative predictive value for the diagnosis of IPF in many patients. In patients without an environmental exposure history or evidence of a collagen vascular disease, an HRCT pattern suggestive of IPF even in the absence of honeycombing has a high positive predictive value for IPF and a lung biopsy is considered unnecessary (Raghu, 2014). A recent analysis of the INPULSIS trial further substantiates that IPF in patients with and without honeycombing on HRCT behave similarly. In the INPULSIS trials, there was no difference in the rate of decline in FVC between patients with and without honeycombing who received placebo. Furthermore, there was no difference in the treatment response to nintedanib among patients with and without honeycombing (Raghu, 2017).

A Fleischner Society White paper on the diagnostic criteria of IPF was recently published (Lynch, 2018). In this paper, a new category in the interpretation of HRCT patterns, "Computerized tomography (CT) pattern indeterminate for usual interstitial pneumonia (UIP)," was proposed to encompass an HRCT that may be consistent with IPF and that lacks features most consistent with a non-IPF diagnosis. This new category can be considered a refinement of the 2011 ATS/ERS/JRS/ALAT criteria (Raghu, 2011), in which an HRCT classified as "inconsistent with UIP" did not distinguish between patients whose scans were insufficient to secure this diagnosis in the absence of additional information (eg, lung biopsy), from patients who were unlikely to have IPF.

Based upon the findings cited above, the incorporation of the modified IPF algorithm will permit the inclusion of those patients diagnosed with IPF who would not have qualified for the current study under the 2011 ATS/ERS/JRS/ALAT guidelines (Raghu, 2011).

In addition, lung cryobiopsy was added as an alternative diagnostic tool to surgical lung biopsy (SLB) since pathologic analysis of lung cryobiopsy showed that a UIP pattern identified using the same criteria used when analyzing the SLB samples may be identified with high confidence in almost 80% of the cases and the interobserver consistency is similar to that obtained with surgical specimens (Colby, 2017).

- Revised inclusion criterion number 8 to clarify that transbronchial biopsy, bronchoalveolar lavage (BAL), or surgical lung biopsy (SLB), must have been performed prior to Screening.
- Revised inclusion criterion number 9 and Protocol Summary Study Population to include an upper limit for percent predicted forced vital capacity (% FVC) of ≤ 95%.

  Including a cap for the upper limit of % predicted FVC will exclude rare, atypical IPF subjects from the study who are unlikely to demonstrate a treatment benefit, regardless of the treatment.

  - Revised inclusion criterion number 11 and Protocol Summary Study Population regarding the upper limit for hemoglobin-corrected $D_LCO$.

    In response to recommendations of several investigators, the upper limit for hemoglobin-corrected percent predicted $D_LCO$ was changed from 85% to 90% predicted.

- **Exclusion Criteria (Section 4.3)**
  - Clarified in exclusion criterion number 10 that lung transplantation should not occur within the first 24 weeks of the study.

    Since it is difficult to predict when a subject will receive a lung transplant while participating in the study, the study will only exclude those subjects who are expected to be transplanted before Week 24 (the time when the primary endpoint is assessed).
  - Revised exclusion criterion number 12 regarding IPF targeted therapies.

    Mycophenolate mofetil was added to the list of excluded medications as it may be used off-label to treat IPF. This revision is also reflected in Sections 8.1.3 and 8.3.1 in the protocol.
  - Revised exclusion criterion number 13 regarding cytokine modulators/biologics.

    Revised criterion to include the term "biologic" as rituximab is a biologic that targets B cells, rather than a cytokine.
  - Removed exclusion criterion number 15 regarding supplemental oxygen use.

    Use of continuous supplemental oxygen is considered standard practice for many IPF patients in parts of the world located at higher altitudes.
  - Clarified that exclusion criterion number 20 regarding history of hepatitis B and /or hepatitis C applies even to those subjects who were considered successfully treated/cured.

    Currently it is unknown if CC-90001 has the potential to reactivate the hepatitis B and /or hepatitis C viruses.

- **Revised the Protocol Summary Study Treatments, Section 7.2 Treatment Administration and Schedule, and Section 7.2.3 Method of Treatment Assignment**
  - Sections were revised to reflect an 80-week Active Treatment Extension Phase; clarified how the subjects who received placebo in the 24-week Treatment Phase will be provided active drug in the 80-week Active Treatment Extension Phase, and revised the timing and the number of blister cards to issue in the 80-week Active Treatment Extension Phase (Section 7.2 only).
  - Described how the subjects that were enrolled under Protocol Amendment 1.0 will continue in the study under Protocol Amendment 2.0.

- Revised the number of blister cards to be dispensed based upon the 80-week Active Treatment Extension Phase.

- **Revised Section 1.7.8 Potential Risks of CC-90001 and the Study Population**

  A description of why statins require close monitoring while subjects are on the study was added.

- **Revised text in Section 8.1 Permitted Concomitant Medications and added New Section 8.2.1 Statins**

  New preliminary data suggest that CC-90001 is an inhibitor of three transporters, organic anion transporting polypeptides (OATP1B1 and OATP1B3) and breast cancer resistance protein (BCRP). Concomitant use of a statin with CC-90001 may increase plasma concentrations of statins. Therefore, to ensure the safety of the subjects taking statins concomitantly with CC-90001 the procedure for how statins are to be dosed on the study is described in the protocol.

- **Revised Section 8.1.1 Permitted Concomitant Medications Throughout the Study**

  Added new bullet to further describe the use of oral corticosteroids in the study.

- **Revised Section 11.1 Treatment Discontinuations**

  The term "Disease progression" was substituted for "Absolute decrease of ≥ 10% from baseline in percent predicted FVC at two consecutive evaluations at a minimum of 4 weeks between evaluations." The revised text clarifies that evidence of disease progression other than decrease in FVC (e.g., worsening hypoxemia or a decrease from baseline in 6-minute walk test (6MWT) distance, as defined in Table 2, Study Endpoints) may be reasons to discontinue treatment at the Investigator's discretion. However, "Absolute decrease of ≥ 10% from baseline in percent predicted FVC at two consecutive evaluations at a minimum of 4 weeks between evaluations" remains a mandatory requirement for treatment discontinuation.

- **Revised Section 11.2 Discontinuation Criteria for Elevation of Hepatic Transaminases**

  [redacted] it was clarified in Section 11.2 that subjects who experience elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x upper limit of normal (ULN) should also have repeat testing that includes AST, ALT, total bilirubin, and alkaline phosphatase testing and that the elevated hepatic enzymes should be followed until resolution.

- **Revised the Table of Events, Table 4**

  To be consistent with the 80-week Treatment Extension, the visit spacing and timing of some of the assessments were revised (vital signs, weight, electrocardiogram, clinical labs, [redacted] St. George's Respiratory Questionnaire (SGRQ), [redacted] spirometry, arterial oxygen saturation by pulse oximetry ($SpO_2$), $D_LCO$, 6MWT, assessment of shortness of breath, [redacted] and return of investigational product [IP]). The abbreviations in the table were also revised to reflect the revised table.

**Protocol Template Revisions**

- To comply with the latest protocol template revisions, the following items were addressed in the protocol:
  - Added to Section 3.1 the additional language to document blinding status of the study team roles.
  - Moved Patient-reported Outcomes description to the newly defined Section 6.7. As a result of this template change, several sections within Section 6 required new sub-section renumbering.
  - Added Section 15.3 Product Quality Complaint to provide information to investigators regarding the definition of a product quality complaint (PQC) and how to notify the Sponsor of a suspected PQC.

**The amendment also includes other minor clarifications and corrections including:**

[redacted]

- Section 1.6 was revised to remove 400 mg PO QD dose as this hypothesis should include both studied doses.
- Sections 1.7.2 and 1.7.5 were revised to reflect the 80-week treatment extension where all subjects will be receiving active CC-90001.
- Removed "inhaled steroids" from the list of excluded IPF targeted therapies as inhaled corticosteroids are permitted for use throughout the study.
- Revised parts of Section 6.1, Screening Phase:
  - Clarified that subjects who were previously vaccinated for hepatitis B are eligible for the study.
  - Removed the verbiage regarding the order of the assessments.
  - Revised the HRCT diagnosis criteria according to Lynch, 2018. Rationale for this change is described above, under inclusion criterion number 6 and Table 3.
  - Postmenopause test: Estradiol and follicle-stimulating hormone (FSH) levels are required for all females who have not had a menses for at least one year, and do not have documentation confirming their postmenopausal status. The original text mentioned females 50 to 55 years of age. Because females can reach menopause in their forties, the language was simplified to address all females who have not had a menses for at least one year.
  - Revised Section 6.1 to reflect 8 weeks of the Baseline visit.

[redacted]

- Clarified text related to treatment administration in Section 7.2.
- Revised the timeframe for the overdose definition in Sections 7.2.1 and 7.2.2. Overdose is defined within the same calendar day and no longer within a 24-hour period as ingestion of "> 2 tablets within the same calendar day" instead of "> 4 tablets within a 24-hour period". To be consistent with the revised definition of overdose, the window of time of when an IP dose could be taken within the same day was changed from "12 hours" to "36 hours" from the previous dose taken.
- Table of Events and Section 7.2.3 were revised to read 80-week Active Treatment Extension Phase.
- Clarified in Table 4 footnote c that pregancy testing during the 80-week treatment extension for females of childbearing potential will be done as an unscheduled visit.

[redacted]

- Revised the statistical Sections 9.1, 9.6.2.2, and 9.7 to reflect the 80-week Active Treatment Extension Phase.
- Revised Section 9.2 to comply with new protocol deviation convention and to further define the Full Analysis Set (FAS).
- Clarified in Section 9.6.1 why there is no adjustment for multiplicity.
- Revised Section 9.8 to reflect the timing of the interim analysis to occur when 40% to 50% of subjects complete 24 weeks of treatment.
- Revised Sections 11.1 and 11.3 last bullet to read important protocol deviation to comply with new protocol deviation convention.
- Renamed the table for Selected Transporters in Appendix H, and provided an additional table that provides examples of substrates of one or more transporters with a narrow therapuetic index.
- Updated the email addresses for the [redacted] personnel
- Minor editorial changes

**New references cited in the protocol:**

Chung J H, Oldham JM, Montner SM, Vij R, Adegunsoye A, Husain AN, et al. CT-pathologic correlation of major types of pulmonary fibrosis: insights for revisions to current guidelines. AJR Am J Roentgenol. 2018;210:1034-41.

Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JG, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138-153.

**References cited above:**

Colby TV, Tomassetti S, Cavazza A, Dubini A, Poletti V. Transbronchial cryobiopsy in diffuse lung disease. Update for the pathologist. Arch Pathol Lab Med. 2017;141:891-900.

King TE Jr. Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370(22):2083-92.

Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. Clin Epidemiol. 2013; 5: 483-92.

Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JG, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138-153.

Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183: 788-824.

Raghu G, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, et al. Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. Lancet Respir Med 2014;2(4):277–84.

Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, et al. Effect of nintedanib in subgroups of idiopathic pulmonary fibrosis by diagnostic criteria. Am J Respir Crit Care Med. 2017;195(1):78–85.

Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl J Med.2014; 370:2071-82.

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Inclusion Criteria (Section 4.2)**
  - Added new inclusion criterion #4 regarding consideration of treatment options for idiopathic pulmonary fibrosis (IPF)

    **"**Investigator has considered all available IPF treatment options with the potential subject before consenting the subject for participation in the study**"**

    [redacted]
  - Revised inclusion criterion #6 regarding the diagnosis of IPF via high resolution computerized tomography (HRCT)

    Increased the time prior to randomization for acceptance of historical HRCT from 12 months to 18 months.

    This change in the window for use of a historical HRCT reflects standard practices in many regions regarding the frequency of HRCT for IPF patients, particularly in those regions that do not permit periodic HRCT due to radiation restrictions (eg, Germany).
  - Revised inclusion criterion #11 and Protocol Summary regarding the lower limit for diffusion capacity of the lung for carbon monoxide ($D_LCO$)

    In response to recommendations of investigators, the lower limit for hemoglobin-corrected percent predicted $D_LCO$ was changed from ≥30% to ≥ 25%.

    A substantial number of patients with IPF may have forced vital capacity (FVC) values of 45% predicted or greater but with relatively low $D_LCO$ (eg, in the 25% to 30% predicted range). Increasing the range of acceptable $D_LCO$ by reducing the lower limit to of ≥ 25% predicted $D_LCO$ will enable recruitment of IPF patients to more closely reflect the spectrum of IPF who might be eligible for treatment. The amended protocol also clarifies that percent predicted $D_LCO$ values used will be corrected for hemoglobin, to better standardize this measurement.

- **Exclusion Criteria (Section 4.3)**
  - Revised exclusion criterion #9 regarding respiratory disorder

    Added to the term pulmonary arterial hypertension, requiring treatment to exclude those patients with more advanced disease.
  - Revised exclusion criterion #12 regarding IPF targeted therapies

    Mycophenolate mofetil was added to the list of excluded medications as it may be used off-label to treat IPF.

- Revised exclusion criterion #13 regarding cytokine modulators/biologics

  Revised criterion to include the term biologic as rituximab is a biologic that targets B cells, rather than a cytokine.

  Alefacept was removed from the list of cytokine modulators as it is no longer a marketed drug.

- Revised exclusion criterion #15 regarding supplemental oxygen use

  Clarified that subjects who receive continuous supplemental oxygen as part of standard of care for all IPF patients residing at high altitudes are not excluded from participation in the trial.

- Clarified in exclusion criterion #19 regarding valve replacement

  Replaced the term "artificial" with "cardiac" valve replacement requiring anticoagulation therapy.

- Revised exclusion criterion #29 regarding use of smoking products

  Revised this criterion to exclude subjects who smoke pipes, cigars, vapes, e-cigarette and marijuana, in addition to cigarettes.

- **Included External Data Monitoring Committee (DMC) (Section 9.9.3 and Protocol Summary)**
  - [redacted] the internal DMC was replaced by an external DMC.

[redacted]

- **Mandatory Discontinuation Due to Unsuccessful Treatment of Acute Exacerbation (Sections 8.1.2 and 11.1)**
  - The duration of time required for mandatory discontinuation due to unsuccessful treatment of acute exacerbation was increased from 2 weeks to 6 weeks. This change was recommended by multiple study investigators, who stated that many patients with an acute IPF exacerbation who eventually recover do not begin to demonstrate improvement within a 2-week time period.
- **Revised the Discontinuation Criteria for Elevated Liver Function Tests (Sections 1.7.8, 6.2, and 11.2)**
  - [redacted] the fold-elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) requiring withholding study drug and potential discontinuation was lowered. The reference

to the DHHS guidance document was removed from Sections 1.7.8 and 17 in the protocol.

[redacted]

- **6-minute walk test (6MWT) (Appendix E)**
  - Study investigators requested that the 6MWT to follow be included as an appendix in the protocol. This will ensure greater uniformity in how the 6MWT is performed across sites. Added new reference in Section 17, American Association for Respiratory Care. Clinical practice guideline. Exercise testing for evaluation of hypoxemia and/or desaturation. Respir Care 1992;37:907–912.

**The amendment also includes other minor clarifications and corrections including:**

- Corrected the title of the Celgene Therapeutic Area Head Signature page to read Clinical Research and Development, Immunology and Inflammation.
- The medical monitors originally assigned to the protocol to cover the Americas, Canada, European Union and Asia Pacific were replaced due to a change in personnel at the clinical research organization (CRO).
- Corrected Table 4, Visit 9 to have a ± 3-day visit window.
- Removed the sentence that incorrectly references the cough domain in the Saint Georges Respiratory Questionnaire in Sections 1.7.7 [redacted] and in Table 2.
- Further clarified in Section 6.1 and Table 4, that in the event that a historical HRCT does not meet study eligibility (as determined by the central reader), a new HRCT must be obtained. For sites subject to regulatory restrictions that do not permit HRCT within this time period, a previous HRCT scan is permissible if it meets image acquisition guidelines and scan is reviewed by centralized review. Note: HRCT should be obtained after the subject has satisfied all of the above study assessments for study eligibility.
- Further clarified in Section 6.1, how minor fluctuations of symptoms (eg, cough and dyspnea) that reflect the underlying disease should not necessarily be recorded as an adverse event (AE) if they are similar in intensity and duration to prior such fluctuations. More marked and or sustained worsening of such symptoms should be recorded as an AE.
- Further clarified in Section 6.1 how positive hepatitis test results should be interpreted for those subjects who have been previously vaccinated for hepatitis B.

[redacted]

- Corrected Section 7.2, Treatment Administration and Schedule and Table 4 for the visit timing and number of blister cards dispensed based upon drug configuration cards.
- Further clarified in Section 7.2.2, that if investigational product (IP) is missed and the timing occurs > 12 hours of the previous dose, the dose should be skipped.

[redacted]

- Corrected Section 12.2 for emergency unblinding of study IP, that it will occur via the Interactive Web Response System (IWRS).
- Replaced the Borg scale in Appendix F with copyrighted version.
- Clarified in the following sections that $D_LCO$ will be hemoglobin-corrected: Study population in the Protocol Summary, Table 2, inclusion criterion #11, Sections 6.1 and 6.5.2.2.
- Clarified in Table 4 and Sections [redacted] 6.1 and 8.2 that warfarin is but one example of a vitamin K antagonist; in some countries, other vitamin K antagonists can be used instead.
- Clarified in Sections 1.7.8 and 6.1 that the cholesterol panel will include total, high density lipoprotein (HDL) and low density lipoprotein (LDL).
- Changed centralized to independent adjudication committee in Section 3.1.1 and Protocol Summary.
- Added in Section 8.2 a reminder to investigators to contact the sponsor if they have any question regarding the administration of CC-90001 with drugs that are substrates for the transporters described in this section.
- Added in Section 8.3.1 that marijuana should not be used within 3 months of Screening.
- Further clarified in Section 8.3.2 that oral anticoagulants for conditions other than IPF (with the exception of cardiac valve replacement) are permitted.