Protocol for

Official Title of Study

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, DOSE-FINDING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-90001 IN SUBJECTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND LIVER FIBROSIS

NCT04048876

April 16, 2021

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PROTOCOL NUMBER:	**CC-90001-NASH-001**
DATE FINAL:	**01 Mar 2019**
DATE AMENDMENT 1 FINAL:	**23 May 2019**
DATE AMENDMENT 2 FINAL:	**26 Sep 2019**
DATE AMENDMENT 3 FINAL:	**11 Nov 2020**
DATE AMENDMENT 4 FINAL:	**16 Apr 2021**
EudraCT NUMBER:	**2018-004431-79**
IND NUMBER:	**138213**
SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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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.

Back-up 24-hour Global Emergency Contact Call Center:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[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

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ 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

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:** _____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter, Dose-finding Study to Evaluate the Efficacy and Safety of CC-90001 in Subjects with Non-alcoholic Steatohepatitis (NASH) and Liver Fibrosis

Indication

Non-alcoholic steatohepatitis (NASH)

Objectives

The effect of oral (PO) CC-90001, administered once daily (QD), compared with placebo, will be evaluated in subjects with NASH and Stage 2 or Stage 3 fibrosis.

Primary Objective

The primary objective of the study is to evaluate the effect of oral CC-90001, administered QD, compared with placebo, on liver histology in subjects with NASH and Stage 2 or Stage 3 fibrosis.

Secondary Objective(s)

- To evaluate the effects of oral CC-90001, administered QD, compared with placebo, in subjects with NASH and Stage 2 or Stage 3 fibrosis, on:
  - Additional liver biopsy-based endpoints
  - Liver biochemistry-based endpoints
  - Metabolic parameters-based endpoints
  - Dose response
  - Safety and tolerability
  - Pharmacokinetics (PK)

[redacted]

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, multinational, dose-finding study evaluating the efficacy of treatment with CC-90001, compared with placebo, in NASH subjects with Stage 2 or Stage 3 liver fibrosis. Safety, PK, [redacted] of CC-90001 compared to placebo will be evaluated.

Approximately 180 adult male and female subjects with a confirmed diagnosis of NASH and Stage 2 or Stage 3 fibrosis will be randomized 1:1:1 to treatment with oral CC-90001 (200 mg QD, 60 subjects; 400 mg QD, 60 subjects) or matching placebo (60 subjects) for 52 weeks. Prior to the implementation of Protocol Amendment 4, subjects were also randomized into a 100 mg QD dose group. The subjects who were previously randomized to the 100 mg dose group will remain in the 100 mg dose group throughout the study. It is expected that approximately 10-15 subjects will have been randomized to the 100 mg group at time of implementation of Protocol Amendment 4. Thus, a total of approximately 195 subjects will participate in the study.

Randomization will be stratified by liver fibrosis stage (Stage 2/Stage 3) and by the presence of Type 2 Diabetes Mellitus (DM) (yes/no). To ensure enrollment of a suitable number of subjects with Stage 3 fibrosis, up to 15 subjects with Stage 2 fibrosis may be enrolled per arm. Randomization, treatment assignment and stratification will be managed by an interactive web response system (IWRS).

An independent external data monitoring committee (DMC) will be responsible for review of the interim analyses data and will make recommendations to the Sponsor, who will be responsible for final decision-making. An unblinded interim analysis will be performed after approximately 50% of subjects complete 52 weeks of placebo-controlled treatment phase (as described in the DMC Charter).

Subjects who sign informed consent form (ICF) prior to the implementation of Protocol Amendment 4, will have an option to participate in a double-blind active treatment phase. After 52 weeks of placebo-controlled treatment all placebo subjects will be re-randomized 1:1 by IWRS to the 200 mg, or 400 mg QD dose groups at Week 54. Prior to the implementation of Protocol Amendment 4, subjects were also re-randomized into a 100 mg QD dose group. The subjects who were previously re-randomized to the 100 mg dose group will remain in the 100 mg dose group. Subjects who were initially randomized to active

treatment arms will remain in their assigned dose groups through the end of the double-blind active treatment phase.

Subjects who sign ICF after the implementation of Protocol Amendment 4 will receive treatment in a double-blind placebo-controlled treatment phase only.

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.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

The study population includes adult male and female subjects, ≥18 years of age, with a confirmed diagnosis of NASH and Stage 2 or Stage 3 fibrosis based upon the NASH Clinical Research Network (CRN) Histologic Scoring System and a Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) of 4 or higher, with a score of at least 1 for each of the three components (steatosis, hepatocellular ballooning, and lobular inflammation).

Length of Study

Subjects who sign ICF prior to the implementation of Protocol Amendment 4 and elect not to participate in the active treatment phase, or subjects who sign ICF after the implementation of Protocol Amendment 4:

> The study will have a total duration of up to 66 weeks. The study will consist of an up to 10-week Screening Phase; a 52-week Double-blind Placebo-controlled Treatment Phase; and a 4-week Post-Treatment Observational Follow-up Phase.

Subjects who sign ICF prior to the implementation of Protocol Amendment 4 and elect to participate in the active treatment phase:

> The study will have a total duration of up to 116 weeks. The study will consist of an up to 10-week Screening Phase; a 52-week Double-blind Placebo-controlled Treatment Phase; a 50-week Double-blind Active Treatment 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 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.

Study Treatments

All subjects will be instructed to take 3 tablets once daily, approximately the same time of day (preferably in the morning), with or without food. All IP treatment allocation will be handled by IWRS.

- **52-Week Double-blind Placebo-controlled Treatment Phase:**
  - 100 mg PO QD CC-90001 (for subjects who are randomized prior to implementation of Protocol Amendment 4)

  - 200 mg PO QD CC-90001
  - 400 mg PO QD CC-90001
  - Matching Placebo for 100 mg and 200 mg tablets
- **50-Week Double-blind Active Treatment Phase (only for subjects who participate in the active treatment phase):**
  - 100 mg PO QD CC-90001 (for subjects who are randomized or re-randomized prior to implementation of Protocol Amendment 4)
  - 200 mg PO QD CC-90001
  - 400 mg PO QD CC-90001

Overview of Efficacy Assessments

- NASH CRN histological score (liver fibrosis score and NAS)

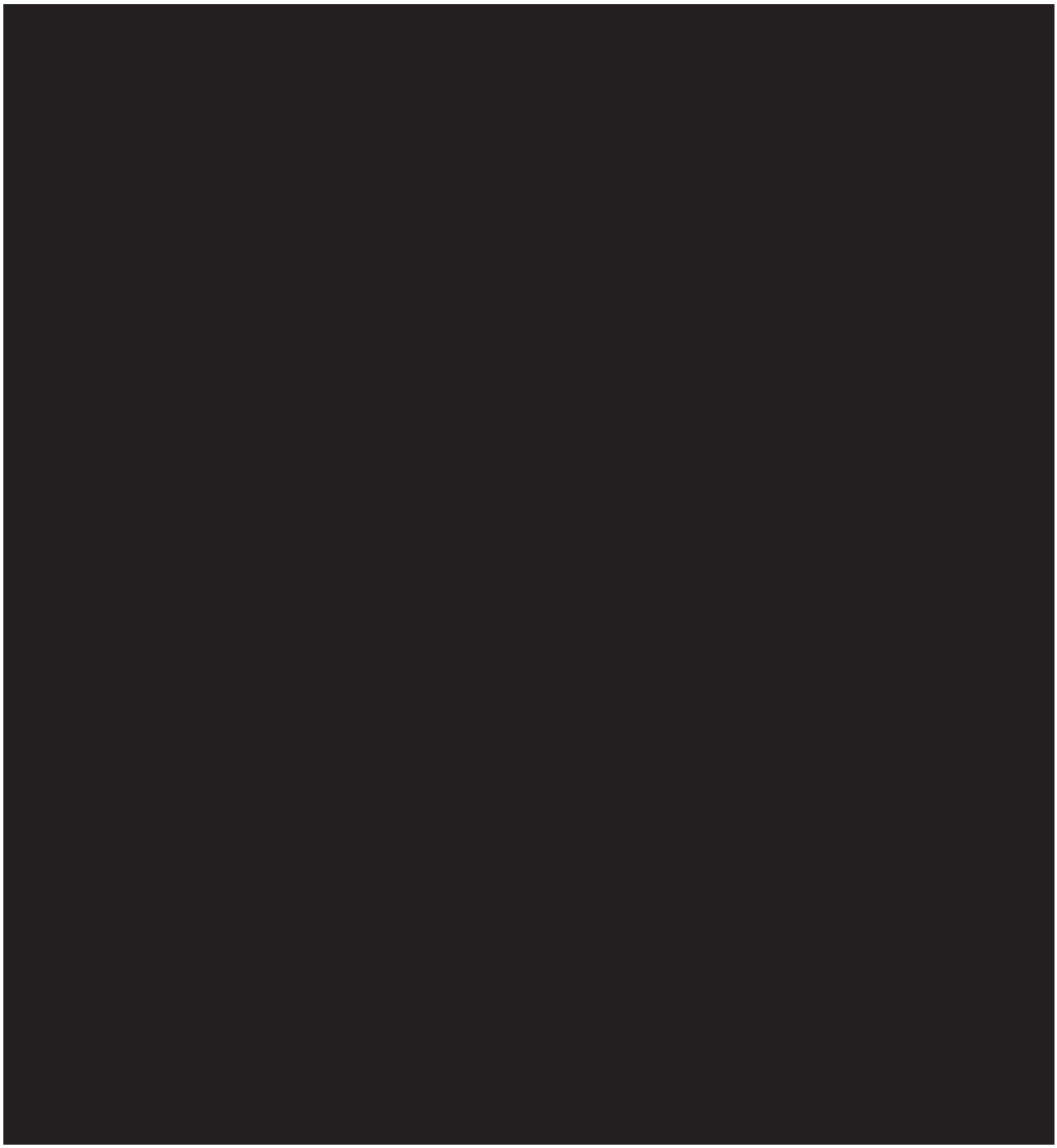
[redacted]

- Liver biochemistry
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Gamma (γ)-glutamyl transferase (GGT)
- Metabolic parameters
  - Serum lipids (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides)

[redacted]

- Progression to cirrhosis (Stage 2 and Stage 3 subjects only)

[redacted]



Overview of Key Safety Assessments

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

- Assessments of concurrent therapies and procedures

Statistical Methods

The estimated improvement on ≥1 fibrosis score in Stage 3 subjects of 45% for CC-90001 group and 20% for the placebo group is based on a Phase 2 study of selonsertib, which reported a 23% treatment difference (43% in the selonsertib 18 mg group versus 20% in the simtuzumab group-a compound that was not demonstrated to be effective for NASH with a treatment response similar to placebo from other clinical trials) (Loomba, 2018; Neuschwander-Tetri, 2015).

With the above assumed treatment responses for the primary endpoint between the highest CC-90001 dose group and the placebo, and further assuming a similar treatment effect in Stage 2 subjects, the sample size of 60 for the placebo, 200 mg, and 400 mg treatment group and an expected sample size of 10-15 for the 100 mg treatment group provides the ability to determine a dose response with 80% power, and 5% type I error rate. It also provides high sensitivity to determine a Minimum Effective Dose (MED) when a range of response rates and clinically significant effects are assumed.

The efficacy analyses will be performed using the Full Analysis Set (FAS), defined as all subjects who are randomized and received at least one dose of IP. The treatment comparison will be made between each of the CC-90001 treatment groups and placebo. No adjustment for multiple comparisons will be made.

The binary efficacy endpoints will be summarized using counts and percentages. The treatment comparisons will be performed using the Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factors as appropriate. Missing values due to early termination will be imputed using data collected at the early termination visit if available; otherwise missing values will be imputed using the non-responder imputation (NRI) method.

The continuous efficacy endpoints will be summarized using mean, standard deviation (SD), median, minimum, maximum, and number of observations analyzed. The treatment comparisons will be performed using a mixed model of repeated measures (MMRM) as the primary analysis method and an analysis of covariance (ANCOVA) model as sensitivity analysis method for all continuous secondary efficacy endpoints. [redacted]

The safety analyses for the 52-week placebo-controlled treatment phase will be performed using descriptive statistics based on the safety population, defined as all subjects who are randomized and receive at least one dose of IP. 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 placebo-controlled treatment phase and active treatment phase.

An unblinded interim analysis will be performed after approximately 50% of subjects complete 52 weeks of treatment (as described in the DMC Charter).

TABLE OF CONTENTS

[redacted]

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LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

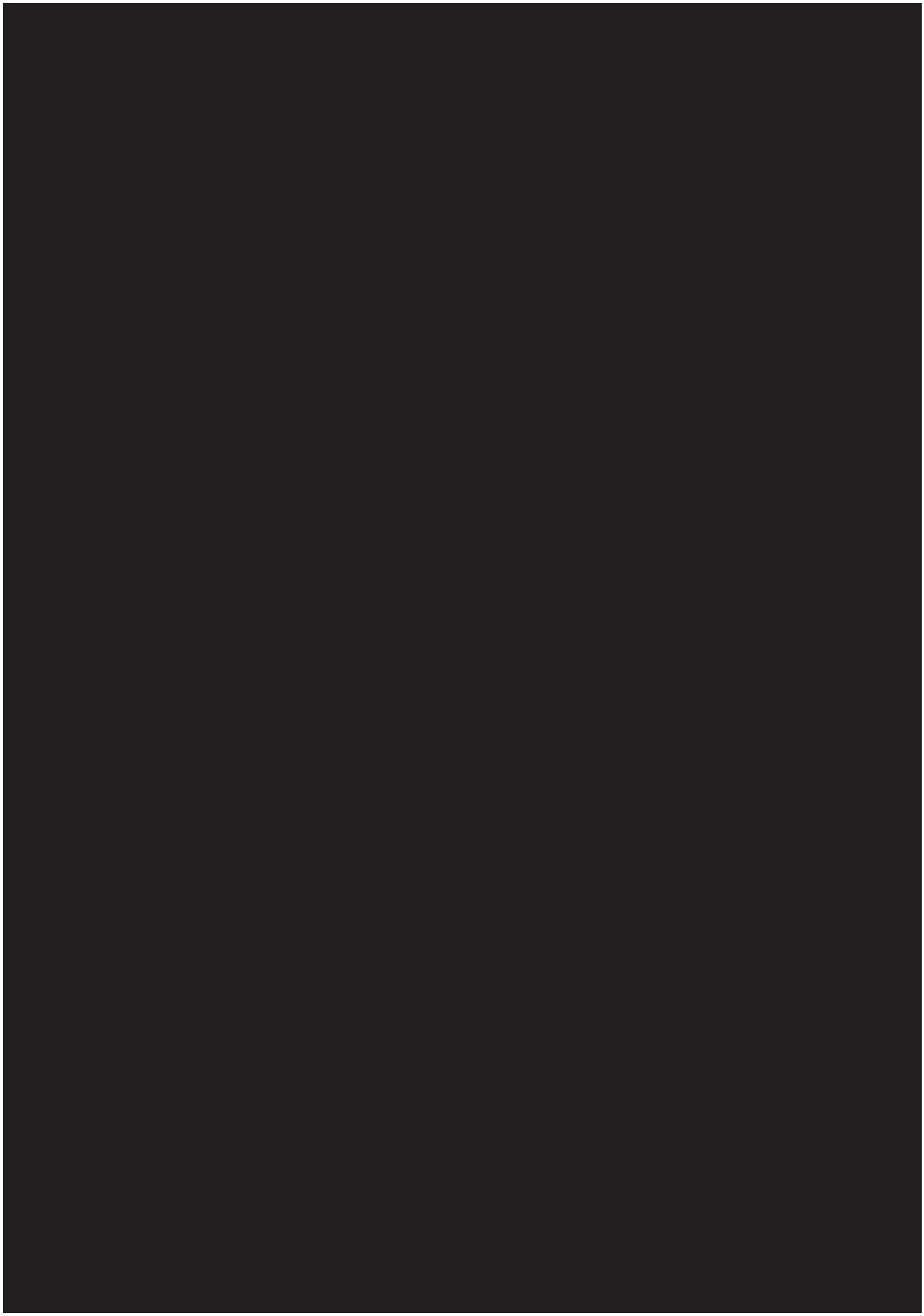
1.1. Disease Background

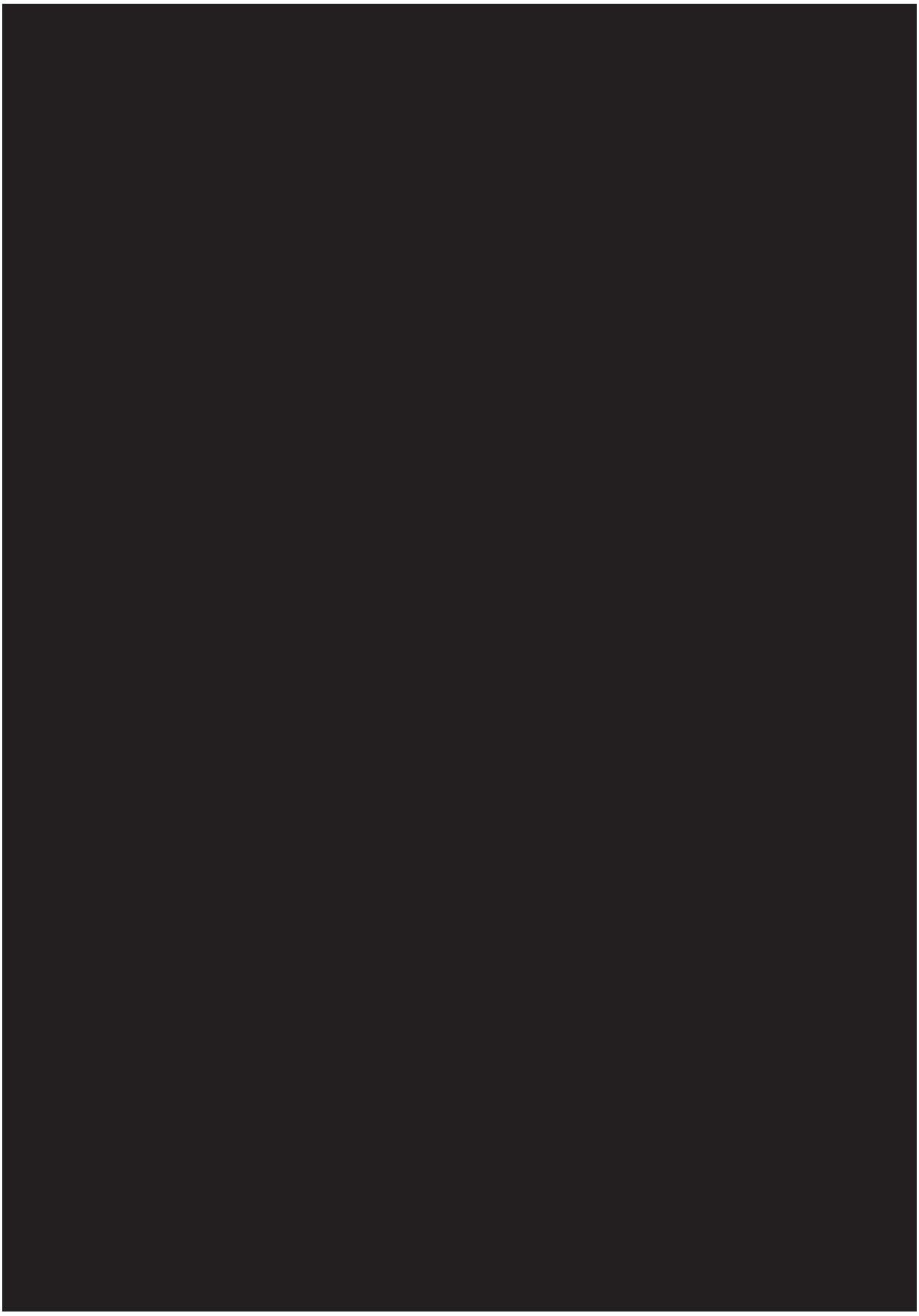
Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, with a global prevalence estimated to be 24% (Younossi, 2018). When steatosis is accompanied by evidence of liver cell injury and cell death, as well as inflammation, it is considered to be nonalcoholic steatohepatitis (NASH). More advanced stages of NASH are accompanied by fibrosis (Diehl, 2017). NASH occurs in approximately 20% of cases of NAFLD and is projected to increase to 27% of NAFLD cases in the US by 2030 (Estes, 2018). Approximately 20% of NASH patients will progress to cirrhosis, with potential complications of portal hypertension and hepatocellular carcinoma (Diehl, 2017). The stage of fibrosis is the most important determinant of mortality in patients with advanced NASH (Hagström, 2017). Patients with NASH and intermediate fibrosis (Stage 2) or advanced fibrosis (ie, Stage 3 and Stage 4 fibrosis) are at a higher risk for liver-related complications and mortality over a relatively short time scale (Sanyal, 2015, Hagström, 2017).

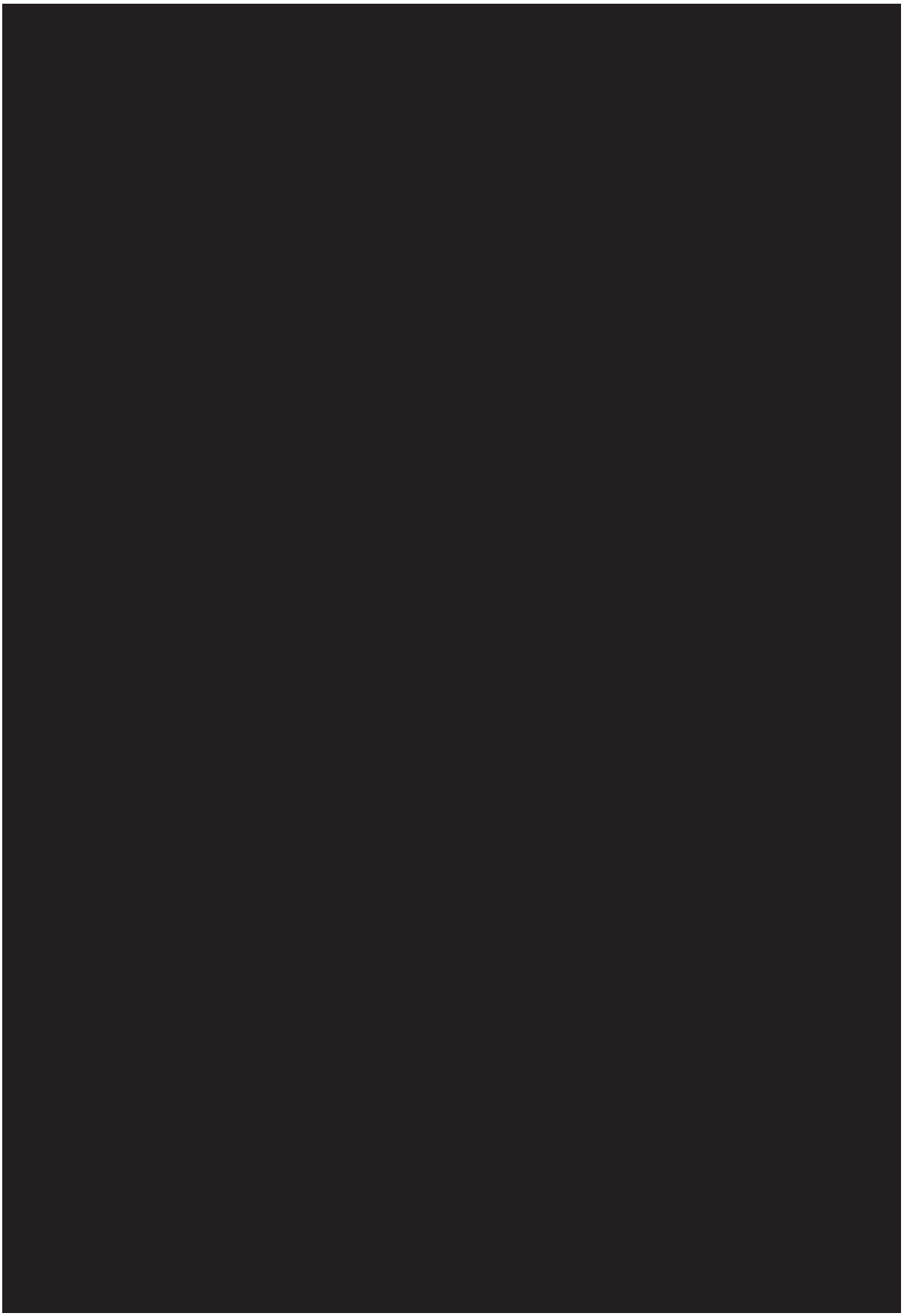
Dietary changes and lifestyle modifications are considered first-line interventions for patients with NASH. Treatments are primarily directed towards improving the metabolic parameters that contribute to disease pathogenesis, such as weight loss and exercise, reducing insulin resistance, and improving diabetic control. Pharmacological options for NASH are outlined in clinical practice guidance or guidelines (European Association for the Study of the Liver [EASL], 2016; Chalasani, 2018). While no firm recommendations are offered, both pioglitazone and vitamin E are suggested treatment options. Treatment with vitamin E or pioglitazone leads to improvement or trends in improvement, respectively, in NASH and both agents are associated with benefits on steatosis and reduction in serum alanine and aspartate aminotransferase levels (Sanyal, 2010). Weight gain is the most common side effect associated with pioglitazone and accelerated bone loss has been reported in women (Chalasani, 2018). Other treatment options that can be considered in individual patients are bariatric surgery, which can lead to improvement or resolution of NASH, and liver transplantation in patients with NASH and end-stage liver disease (EASL, 2016; Chalasani, 2018). NASH is now the most rapidly growing indication for liver transplantation in the United States (Parikh, 2017). Especially in light of the increasing prevalence of NASH, there is an urgent unmet medical need for specific treatments, with a focus on developing treatments that can decrease the progression of NASH and prevent or reverse fibrosis that accompanies NASH.

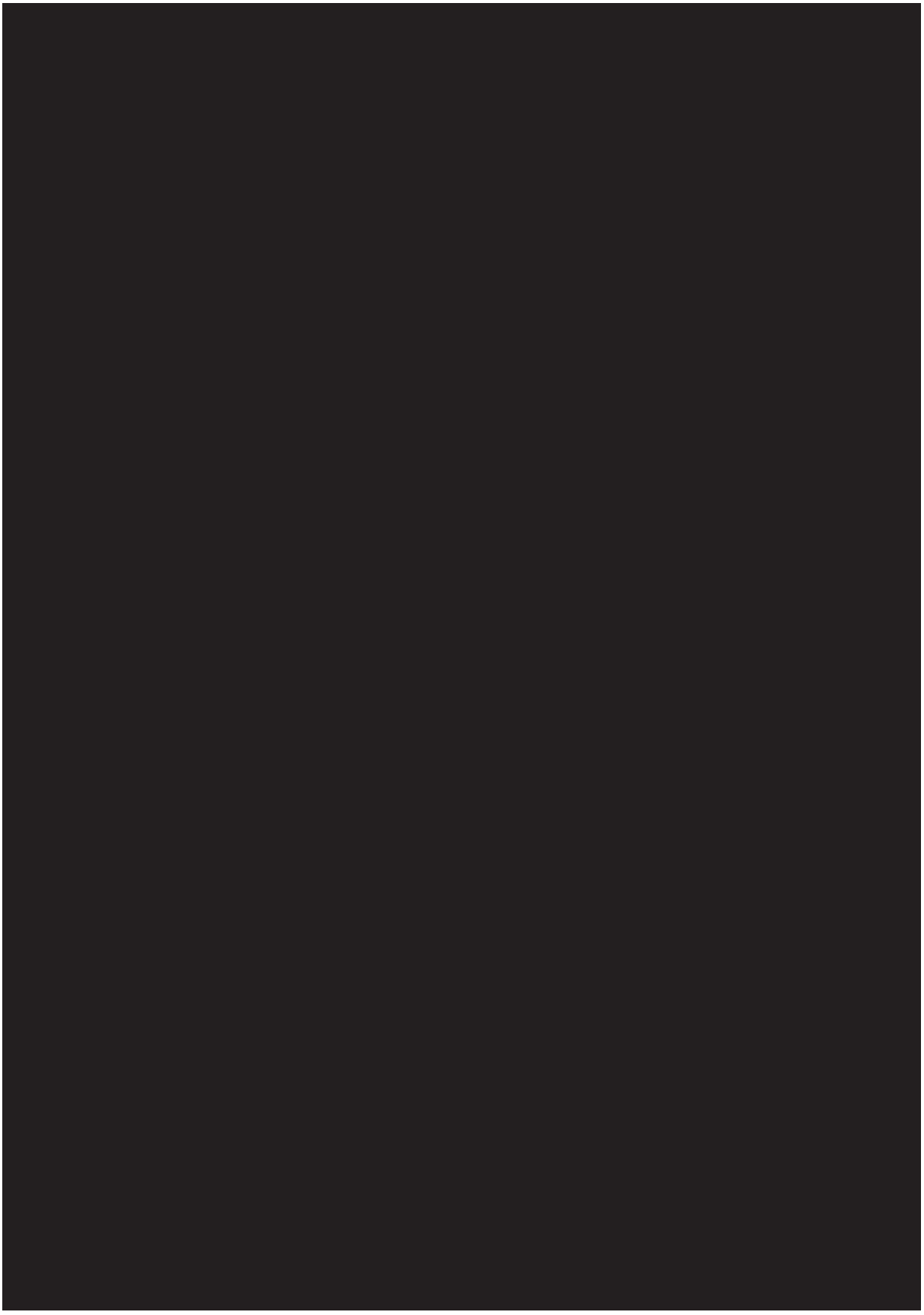
1.2. Compound Background

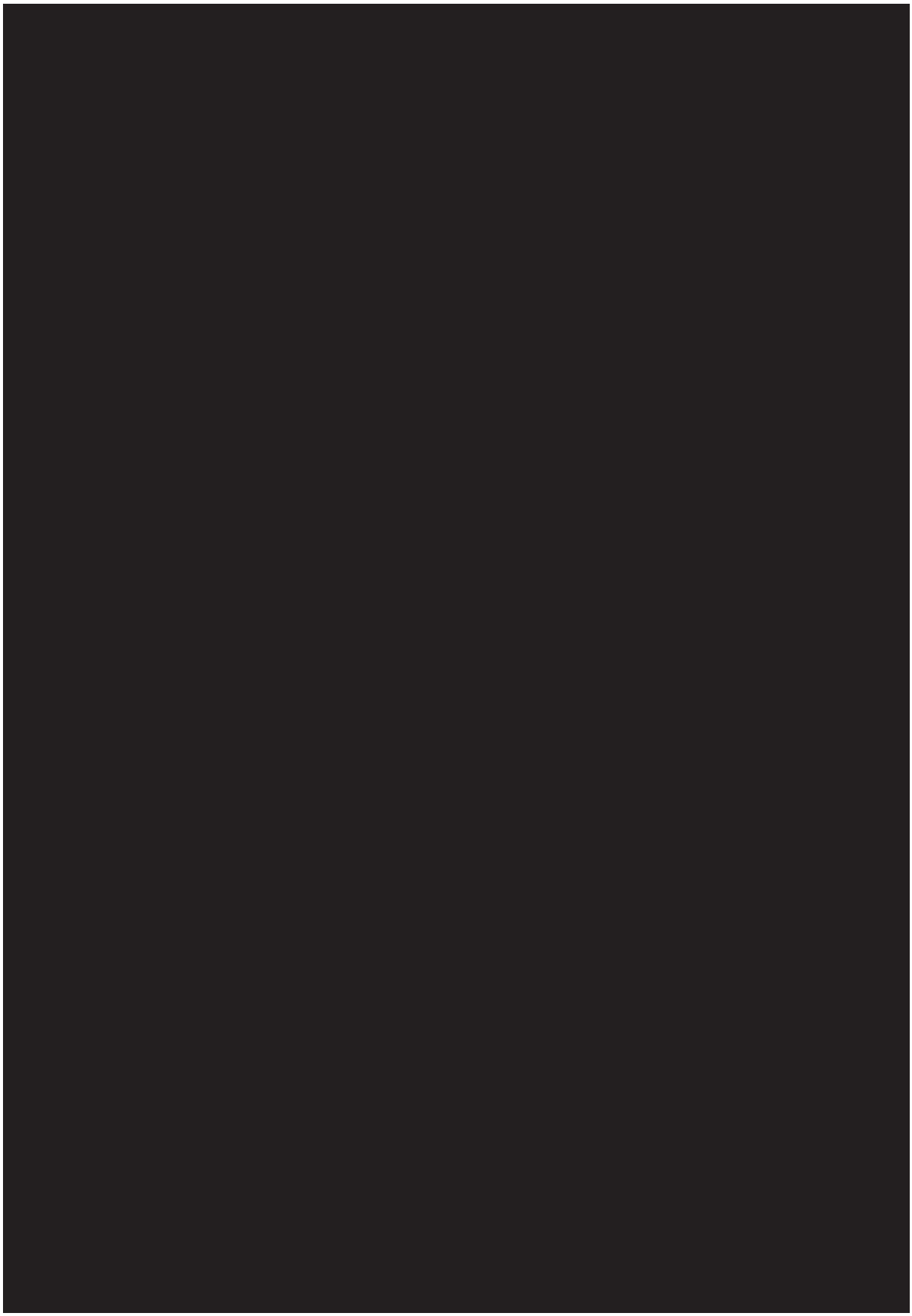
CC-90001 (also known as CC0491359) is a potent and selective inhibitor of c-Jun N-terminal kinase (JNK) [redacted]

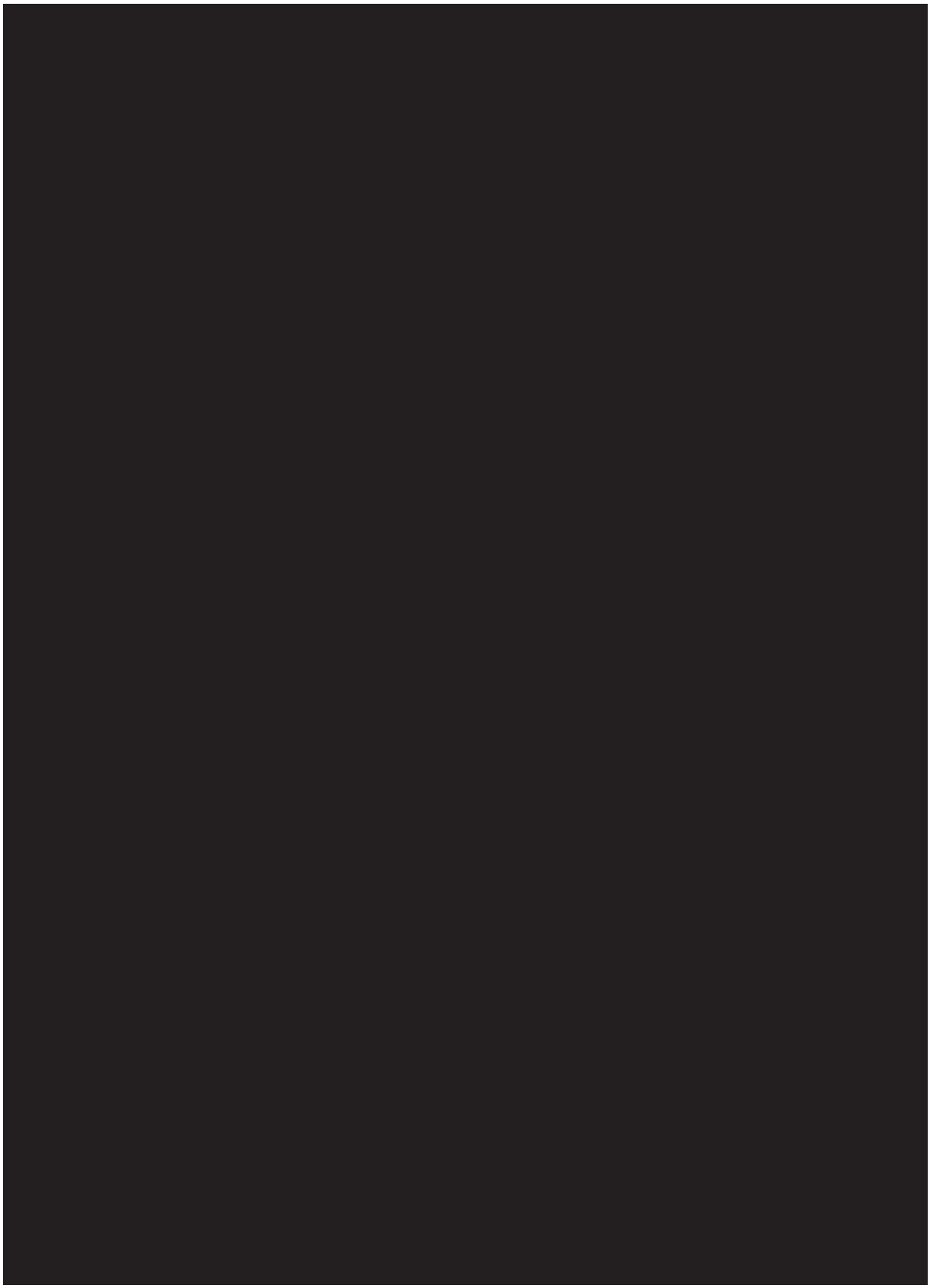


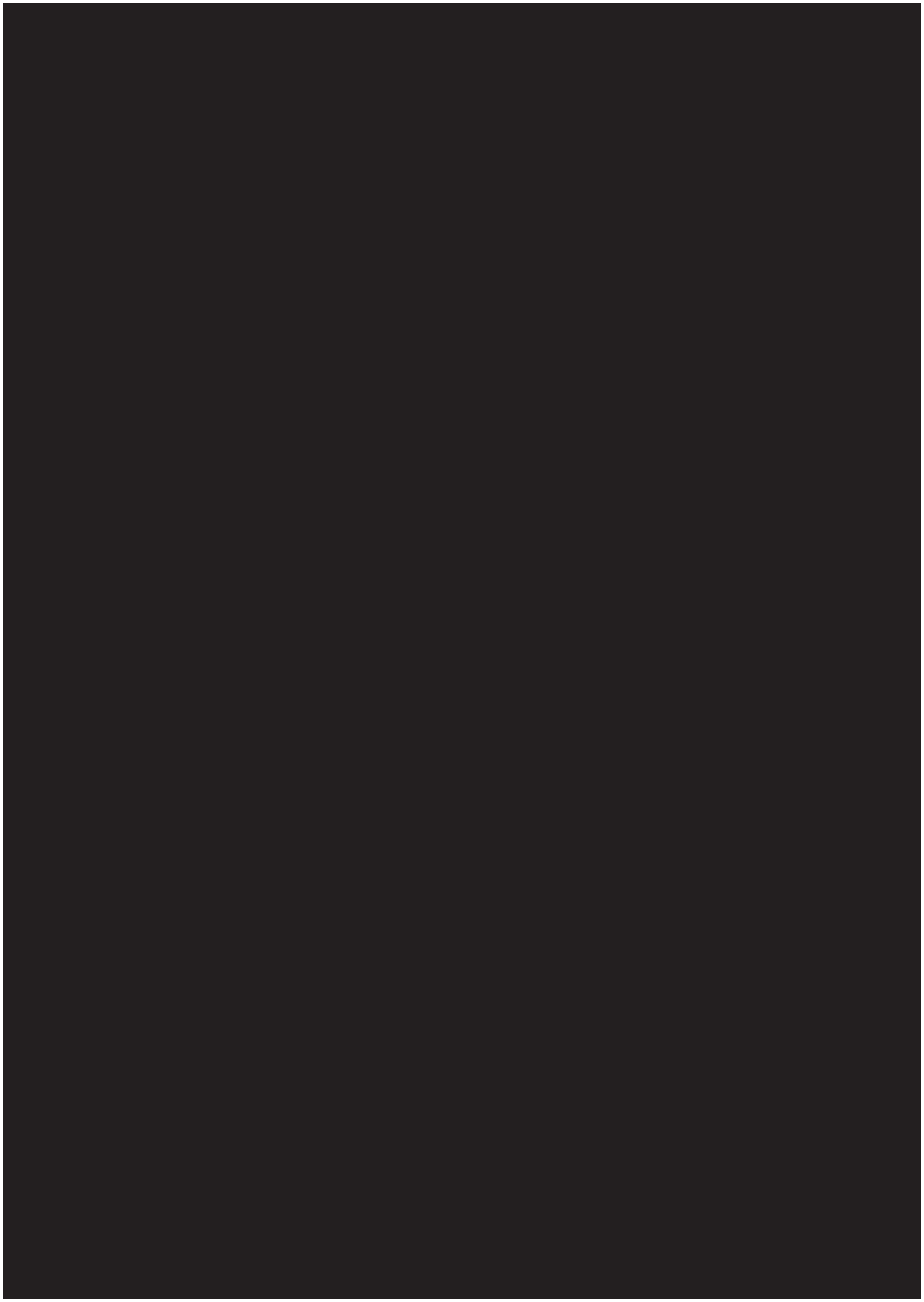












1.3. Rationale

1.3.1. Study Rationale and Purpose

NASH patients who have liver fibrosis comprise the group of patients with both a higher unmet need and potentially reversible disease, given the liver's capacity for regeneration.

Data from pre-clinical models [redacted] support that CC-90001 is potentially effective in patients with NASH and fibrosis. In addition, results from a Phase 2 study of selonsertib, which targets apoptosis signal-regulating kinase 1 (ASK1), provides preliminary evidence that treatment with an anti-inflammatory/anti-fibrotic agent may result in benefits on fibrosis in patients with NASH (Loomba, 2018). Since ASK1 is upstream of the JNK pathway (Win, 2018), CC-90001 as JNK inhibitor may also be an effective treatment in patients with NASH and advanced fibrosis.

The purpose of this study is to evaluate the efficacy and safety of CC-90001 in NASH subjects with either Stage 2 or Stage 3 fibrosis. It is expected that the results from this study will demonstrate a treatment-related difference in the proportion of Stage 2 or Stage 3 subjects who achieve a ≥1 stage improvement in liver fibrosis score at Week 52.

1.3.2. Rationale for the Study Design

CC-90001-NASH-001 is a Phase 2, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of CC-90001 in subjects with NASH and liver fibrosis. Efficacy evaluation will be based on liver biopsy-based endpoints [redacted].

Liver biopsy is widely considered as the "gold standard" for assessing fibrosis in NASH and has been validated in a large cohort of NASH patients (Kleiner, 2005). The primary efficacy endpoint will be the proportion of Stage 2 or Stage 3 subjects who achieve a ≥ 1 stage improvement in liver fibrosis score. The primary efficacy endpoint will be evaluated at Week 52 to allow slowly reversible subjects the opportunity to demonstrate a treatment benefit. Other liver biopsy-based endpoints, such as Non-alcoholic Fatty Liver Disease Activity Score (NAS) for evaluation of steatohepatitis and combination assessment of liver fibrosis score and steatohepatitis will be assessed as key secondary efficacy evaluations.

[redacted]

Laboratory evaluations, AEs, vital signs, electrocardiograms (ECGs), pregnancy tests and physical examinations will be monitored during the study to evaluate safety.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

The efficacy and safety of 100 mg, 200 mg and 400 mg PO QD doses of CC-90001 will be evaluated in this study. [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the effect of oral CC-90001, administered once daily (QD), compared with placebo, on liver histology in subjects with nonalcoholic steatohepatitis (NASH) and Stage 2 or Stage 3 fibrosis.
Secondary Objective(s)
The secondary objectives are: • To evaluate the effects of oral CC-90001, administered QD, compared with placebo, in subjects with NASH and Stage 2 or Stage 3 fibrosis, on: – Additional liver biopsy-based endpoints – Liver biochemistry-based endpoints – Metabolic parameters-based endpoints – Dose response – Safety and tolerability – Pharmacokinetics (PK)

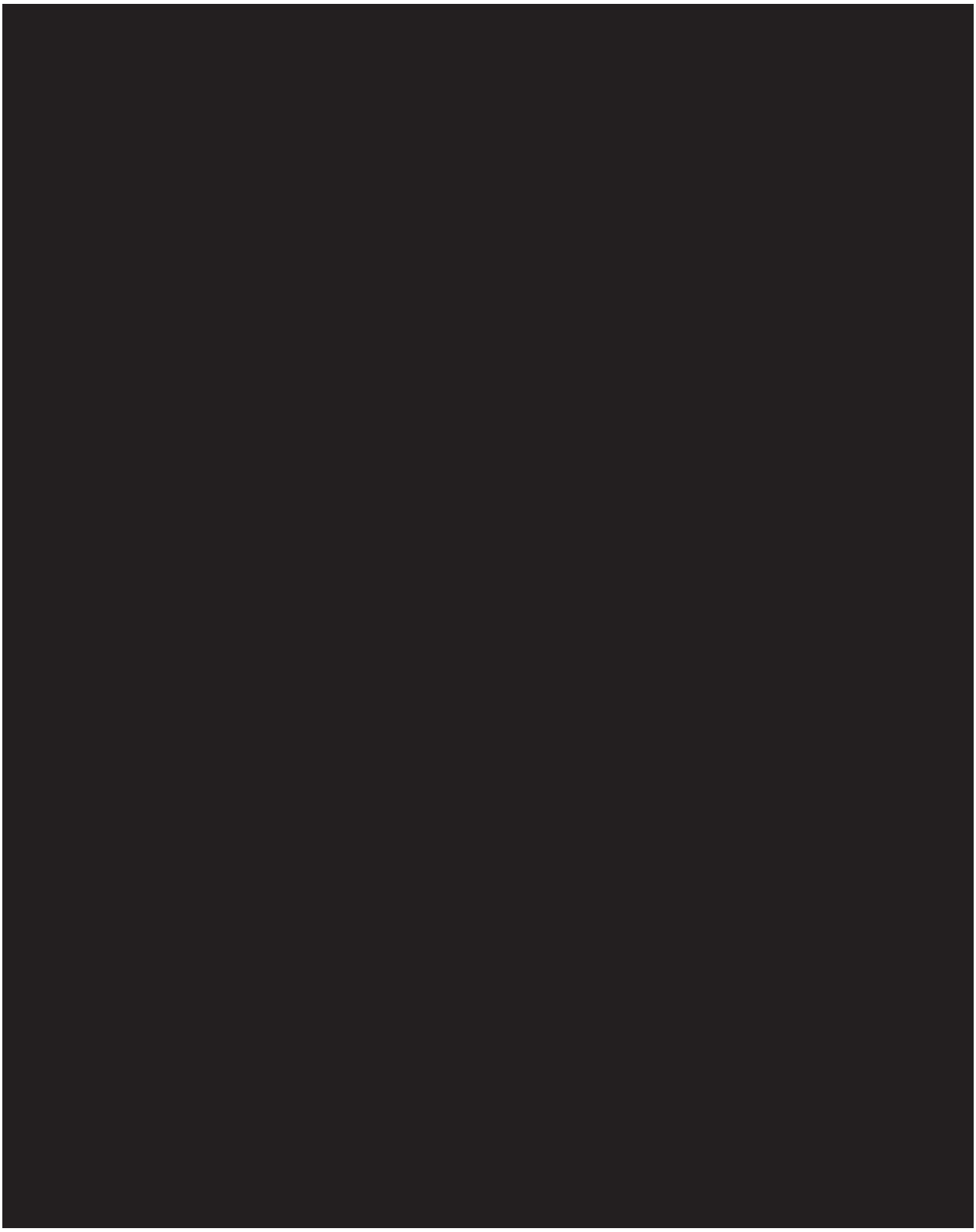
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Liver fibrosis score	Proportion of subjects who achieve a ≥1 stage improvement in liver fibrosis using the nonalcoholic steatohepatitis (NASH) clinical research network (CRN) Histological Scoring System	Week 52
Secondary	Combined assessment of liver fibrosis score and steatohepatitis	Proportion of subjects who achieve a ≥ 1 stage improvement in liver fibrosis and no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning score)	Week 52
	Nonalcoholic fatty liver disease (NAFLD) activity score (NAS)	Proportion of subjects with an improvement of ≥ 2 points in the total NAS in more than one category of steatosis, lobular inflammation, and hepatocellular ballooning, and no worsening of liver fibrosis	Week 52
	Resolution of NASH	Proportion of subjects who demonstrate absence of ballooning, and lobular inflammation score of 0 or 1	Week 52
	Resolution of NASH without worsening of liver fibrosis	Proportion of subjects who demonstrate absence of ballooning, and lobular inflammation score of 0 or 1 and no worsening of liver fibrosis	Week 52
	Progression to cirrhosis	Proportion of subjects who progress to cirrhosis	Week 52
	Liver biochemistry	Change from Baseline in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT)	through Week 52
	Metabolic parameters	Change from Baseline in total cholesterol, low density cholesterol (LDL) high density cholesterol (HDL), and triglycerides	through Week 52
	Dose response	Dose-related changes in the primary and secondary endpoints	through Week 24 (secondary endpoints); through Week 52 (primary and secondary endpoints)

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary	Safety	Type, frequency, severity, and relationship of adverse events (AEs) to CC-90001; Laboratory, 12-lead electrocardiogram (ECG), physical examination or other changes and tolerability	through End of Study
	Pharmacokinetics (PK)	Maximum plasma concentration of drug (C_{max}), area under the plasma concentration time-curve (AUC), time to peak (maximum) plasma concentration (T_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance of the drug (CL/F), apparent volume of distribution (V_z/F), and accumulation index of CC-90001	Day 1 and Week 4
[redacted]			



3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, multinational, dose-finding study evaluating the efficacy of treatment with CC-90001, compared with placebo, in NASH subjects with Stage 2 or Stage 3 fibrosis. Safety, PK, [redacted] of CC-90001 compared to placebo will be evaluated.

This study is designed to assess response to treatment on measures of fibrosis (liver biopsy, [redacted]), [redacted] liver biochemistry, and other efficacy parameters. It will also assess dose response and overall safety.

Subjects who sign ICF prior to the implementation of Protocol Amendment 4 and elect not to participate in the active treatment phase, or subjects who sign ICF after the implementation of Protocol Amendment 4 (Figure 1):

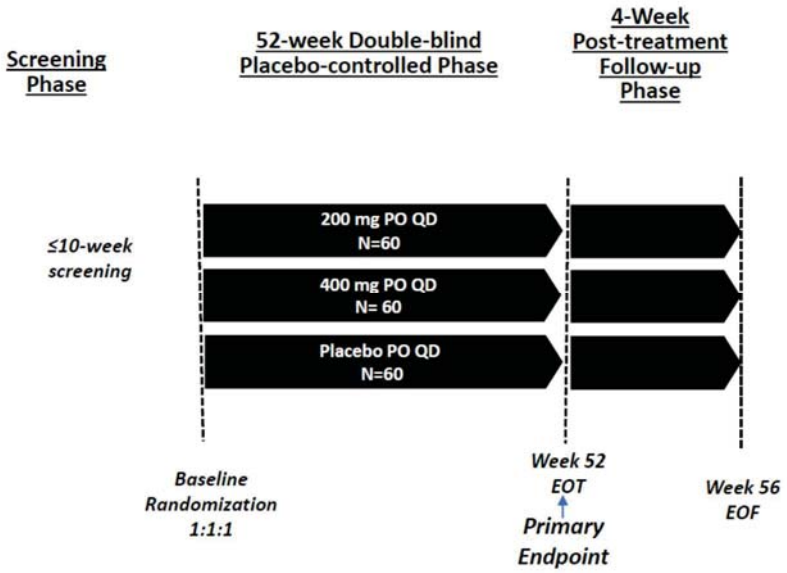
- Screening Phase: up to 10 weeks
- Double-blind Placebo-controlled Treatment Phase: 52 weeks
- Post-treatment Observational Follow-up Phase: 4 weeks

Subjects who sign ICF prior to the implementation of Protocol Amendment 4 and elect to participate in the active treatment phase (Figure 1):

- Screening Phase: up to 10 weeks
- Double-blind Placebo-controlled Treatment Phase: 52 weeks
- Double-blind Active Treatment Phase: 50 weeks
- Post-treatment Observational Follow-up Phase: 4 weeks

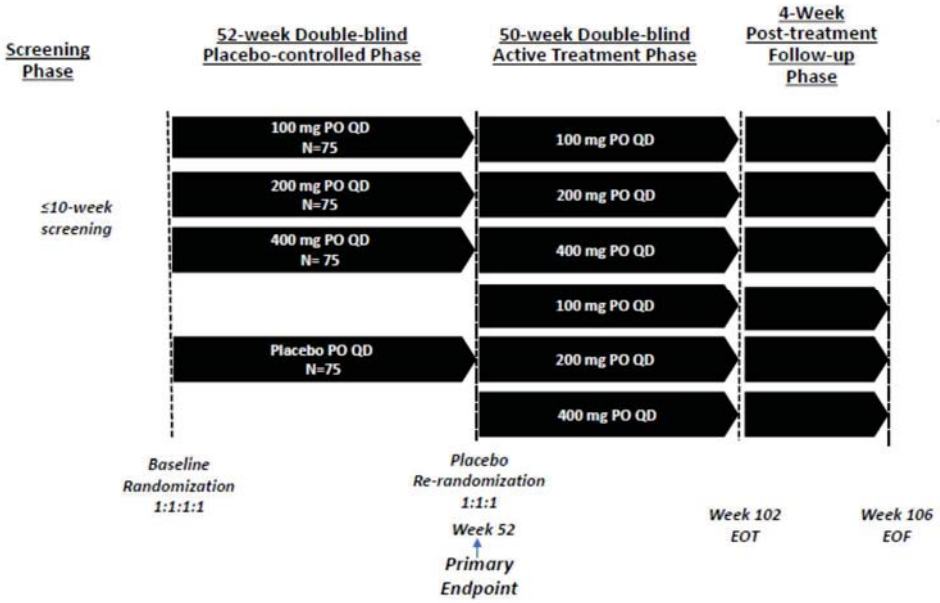
Figure 1: Overall Study Design

After the implementation of Protocol Amendment 4:



Note: The subjects who were previously randomized to the 100 mg dose group will remain in the 100 mg dose group throughout the study. It is expected that approximately 10-15 subjects will have been randomized to the 100 mg group at time of implementation of Protocol Amendment 4.

Prior to the implementation of Protocol Amendment 4:



EOF = end of follow-up; EOT = end of treatment; PO = oral; QD = once daily.

Approximately 180 adult male and female subjects with a confirmed diagnosis of NASH and Stage 2 or Stage 3 fibrosis based upon the NASH Clinical Research Network (CRN) Histologic Scoring System and a NAS of 4 or higher, with a score of at least 1 for each of the three components (steatosis, hepatocellular ballooning, and lobular inflammation), will be randomized 1:1:1 to treatment with oral CC-90001 (200 mg QD, 60 subjects; 400 mg QD, 60 subjects) or matching placebo (60 subjects) for 52 weeks. Prior to the implementation of Protocol Amendment 4, subjects were also randomized into a 100 mg QD dose group. The subjects who were previously randomized to the 100 mg dose group will remain in the 100 mg dose group throughout the study. It is expected that approximately 10-15 subjects will have been randomized to the 100 mg group at time of implementation of Protocol Amendment 4. Thus, a total of approximately 195 subjects will participate in the study.

Randomization will be stratified by liver fibrosis stage (Stage 2/Stage 3) and by the presence of Type 2 Diabetes Mellitus (DM) (yes/no). Approximately 60 subjects with Stage 2 or Stage 3 fibrosis will be enrolled per treatment arm. To ensure enrollment of a suitable number of subjects with Stage 3 fibrosis, up to 15 subjects with Stage 2 fibrosis may be enrolled per arm. Randomization to one stratum will be halted once the enrollment target is achieved for that stratum. Randomization, treatment assignment and stratification will be managed by an interactive web response system (IWRS).

An independent external data monitoring committee (DMC) will be responsible for review of the interim analyses data and will make recommendations to the Sponsor, who will be responsible for final decision-making. An unblinded interim analysis will be performed after approximately 50% of subjects complete 52 weeks of the placebo-controlled treatment phase (as described in the DMC Charter). The DMC will review the totality of the available data to determine the following options:

- Continue the study as planned
- Terminate the study for futility
- Stop enrolling a treatment arm due to futility if not fully enrolled at interim analysis

Subjects who sign informed consent form (ICF) prior to the implementation of Protocol Amendment 4 will have an option to participate in a double-blind active treatment phase. After 52 weeks of placebo-controlled treatment all placebo subjects will be re-randomized 1:1 by IWRS to the 200 mg QD or 400 mg QD dose groups at Week 54. Prior to the implementation of Protocol Amendment 4, subjects were also re-randomized into a 100 mg QD dose group. The subjects who were previously re-randomized to the 100 mg dose group will remain in the 100 mg dose group. Subjects who were initially randomized to active treatment arms will remain in their assigned dose groups through the end of the active treatment phase.

Subjects who sign ICF after the implementation of Protocol Amendment 4 will receive treatment in a double-blind placebo-controlled treatment phase only.

Subjects will have regularly scheduled visits to assess efficacy, safety, tolerability, [redacted] PK [redacted]; refer to Table 3, Table of Events.

All subjects who discontinue prematurely from the study at any time will be required to enter the 4-week Post-treatment Observational Follow-up Phase.

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.

3.2. Study Duration for Subjects

Subjects who sign ICF prior to the implementation of Protocol Amendment 4 and elect not to participate in the active treatment phase, or subjects who sign ICF after the implementation of Protocol Amendment 4:

Subjects will participate for a maximum of 66 weeks in this study, which includes an up to 10-week Screening Phase; a 52-week Double-blind Placebo-controlled Treatment Phase; and a 4-week Post-treatment Observational Follow-up Phase.

Subjects who sign ICF prior to the implementation of Protocol Amendment 4 and elect to participate in the active treatment phase:

Subjects will participate for a maximum of 116 weeks in this study, which includes an up to 10-week Screening Phase; a 52-week Double-blind Placebo-controlled Treatment Phase; a 50-week Double-blind Active Treatment Phase; and a 4-week Post-treatment Observational Follow-up Phase.

3.2.1. Early Termination Visit

The Early Termination (ET) Visit is based on the subject's withdrawal from the study prior to the Week 102 Visit for subjects who participate in the active treatment phase or prior to the Week 52 Visit for subjects who do not participate in the active treatment phase. In addition, the Investigator may discontinue the subject from the study at any time based on his/her assessment of clinical efficacy and/or safety. The decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor. When a subject withdraws or is discontinued from the study treatment, every effort should be made to complete as many safety and efficacy assessments as reasonably appropriate. Refer to the Table of Events (Table 3) for the assessments to be performed at the ET Visit. The ET Visit should be scheduled as soon as possible after the decision is made to permanently discontinue study treatment.

3.2.2. Lost to Follow-up

Subjects will be considered lost to follow-up when they fail to attend study visits without stating an intention to withdraw from the study. The Investigator should show due diligence by documenting in the source documents the steps taken to contact the subject through multiple telephone calls and/or emails and one registered letter. After all reasonable attempts have been made to contact the subject, the subject should be recorded as "lost to follow-up" in the electronic case report form (eCRF).

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 195 subjects with NASH and Stage 2 or Stage 3 liver fibrosis will be randomized worldwide.

4.2. Inclusion Criteria

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

1. Subject is male or female ≥ 18 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. Diagnosis of NASH with presence of Stage 2 or Stage 3 fibrosis based upon central reading of the NASH CRN Histologic Scoring System and a NAFLD Activity Score (NAS) of 4 or higher, with a score of at least 1 for each of the three components (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3) within 6 months prior to Screening or at Screening.
5. If histopathological specimens are submitted from a historical liver biopsy, the subject could not be on a therapy specifically for the treatment of NASH after liver biopsy and the subject's weight must have been documented to be stable since the liver biopsy (ie, within 5% if the liver biopsy was obtained 4 to 6 months prior to Screening or within 2.5% if the liver biopsy was obtained less than 4 months prior to Screening).
6. If receiving any of the following agents, the doses must have been stable for 3 months prior to Screening and the subject must agree to maintain stable doses during the course of the study, unless required to adjust doses due to safety reasons: ursodeoxycholic acid, fibric acid derivatives (fibrates) (eg, gemfibrozil), metformin, sodium-glucose co-transporter 2 (SGLT2) inhibitors (eg, canagliflozin), dipeptidyl peptidase-4 inhibitors ('gliptins') (such as sitagliptin), glucagon peptide-1 (GLP-1) agonists (eg, liraglutide), anti-obesity medications (eg, orlistat, lorcaserin, liraglutide, phentermine-topiramate, or naltrexone-bupropion). Note: If historical liver biopsy is submitted, the doses of above medications must have been stable for 3 months prior to biopsy and stable doses should be maintained through screening and during the course of the study. If SGLT2 inhibitors, GLP-1 agonists and anti-obesity medications have been recently discontinued, the treatment must have been stopped for at least 3 months prior to Screening or historical biopsy used for Screening assessment.
7. If receiving thiazolidinediones (eg, pioglitazone) or vitamin E, the doses must have been stable for 3 months prior to Screening and the subject must agree to maintain stable doses during the course of the study. Note: If historical liver biopsy is

submitted the doses of above medications must have been stable for 3 months prior to biopsy and stable doses should be maintained through screening and during the course of the study. If thiazolidinediones (eg, pioglitazone) or vitamin E have been recently discontinued, the treatment must have been stopped for at least 3 months prior to Screening or historical biopsy used for Screening assessment.

8. Females of childbearing potential (FCBP) [1]must:

    a. Have two negative pregnancy tests as verified by the Investigator prior to starting investigational product (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.

    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 forms of effective birth control (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.

9. 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.

    *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).

[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).

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 (other than NASH related dyscrasias), or psychiatric illness that would confound the ability to interpret data, prevent the subject from participating or place the subject at unacceptable risk if he/she were to participate in the study.
2. History or evidence of decompensated liver disease, including clinical ascites, hepatic encephalopathy, or variceal bleeding.
3. Hepatitis and fibrosis more likely related to etiologies other than NASH such as, but not limited to, alcoholic steatohepatitis, autoimmune hepatitis, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis or iron overload, and drug-induced liver disease.
4. Hemoglobin A1c (HbA1c) ≥ 9.5% at Screening.
5. Subject has evidence of worsening liver function based on two measurements of AST, ALT, alkaline phosphatase (ALP) and total bilirubin (TBL) during Screening period (refer to Section 6.1).
6. Subject has a QTcF > 450 msec.
7. Subject has a history of liver transplantation or subject is likely to have liver transplantation during the study.
8. Current or history of recreational drug abuse or significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening. Significant alcohol consumption is defined as more than 14 oz (420 mL) per week in females and more than 21 oz (630 mL) per week in males, on average (1 oz/30 mL of alcohol is present in one 12 oz/360 mL beer, one 4 oz/120 mL glass of wine, or a 1.5 oz/45 mL measure of 40% proof alcohol).
9. Subject has urine ethyl glucuronide (EtG) > 500 ng/mL at Screening.
10. Use of any drugs that are known to cause hepatotoxicity, such as, but not limited to, acetaminophen (paracetamol) at dosages of > 3 grams/day and niacin at dosages of > 2 grams/day within 2 weeks of randomization.
11. Receiving immunomodulator agents (eg, tumor necrosis factor [TNF] inhibitors), or cytokine inhibitors (eg, tofacitinib) within 3 months of Screening.
12. 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 either hospitalization or treatment with IV 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. Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the clinical trial physician, there are no

sequelae that would place the participant at a higher risk of receiving investigational treatment.

13. History of active or latent tuberculosis (TB), 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 guideline

    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, 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.

14. 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.

15. History or positive screen for human immunodeficiency virus (HIV) infection or congenital or HIV-unrelated acquired immunodeficiencies (eg, common variable immunodeficiency [CVID]).

16. History or positive screen for hepatitis B (See Appendix D) and/or hepatitis C.

    Note: A subject who is hepatitis C antibody (HCV Ab) positive must be excluded unless the subject has a history of HCV and sustained viral response (undetectable HCV ribonucleic acid [RNA]) for at least 2 years prior to Screening and have a negative HCV RNA at Screening.

17. History of cardiac valve replacement requiring chronic anticoagulation therapy

18. History of inflammatory bowel disease (IBD).

19. History of bleeding peptic ulcer or bleeding diverticular disease within the last 5 years.

20. Subjects with Type 1 DM.

21. History of malignancy within the last 5 years (exceptions: excised and cured basal/squamous cell skin carcinomas or cervical carcinoma in situ).

[redacted]

[redacted]

25. Pregnancy or lactation.
26. Subject has a known hypersensitivity to CC-90001 or any ingredient in the investigational product (IP).
27. Concurrent treatment with another IP, including through participation in an interventional trial for COVID-19. Prospective subjects may not participate in a concurrent IP study or have received an IP within 5 drug half-lives prior to screening.
28. Prior use of approved agents for treatment of NASH within 6 months prior to Screening or historical biopsy used for Screening.
29. Subject has a history of bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass) within 5 years prior to Screening or subject is likely to have bariatric surgery during the study.
30. Evidence of the following abnormal laboratory values at Screening:
    - Serum ALT ≥ 5 X upper limit of normal (ULN)
    - Serum AST ≥ 5 X ULN
    - Serum ALP ≥ 2 X ULN
    - Serum TBL ≥ 1.3 mg/dL, unless subject has a documented diagnosis of Gilbert's syndrome. Subjects with Gilbert's syndrome must have total bilirubin of ≤ 5× ULN, with direct bilirubin ≤ ULN and no clinical or laboratory evidence of hemolysis
    - Serum albumin < 3.5 g/dL
    - Alpha-fetoprotein ≥ 200 ng/mL (*Note: Alpha-fetoprotein > 20 ng/mL should be discussed with Sponsor to review the evaluation of Hepatocellular Cancer [HCC]*)
    - Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2
    - Hemoglobin < 10 g/dL
    - Platelet count < 140,000/mm^3
    - INR > 1.2
31. Subjects who have received live attenuated SARS-CoV-2 vaccine within 1 month prior to Screening or anticipate the need to be vaccinated with live attenuated vaccine during the study. Further, for subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the Screening, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Clinical Trial Physician.

Subjects who have received a vaccine approved for Emergency Use Authorization may be considered for inclusion, after discussion with the Medical Monitor.

5. TABLE OF EVENTS

Table 3: Table of Events

Year 1 - For all subjects

	Screening Phase	Double-Blind, Placebo-controlled Treatment Phase						Early Termination	Post-Treatment Observational Follow-up Phase
Visit Number	**Screening**	**2 Baseline**	**3**	**4-9 Every 4 weeks**	**10-13 Every 6 weeks**	**14**	**15**	**ET[a]**	**28**
Week	**-10 to 0**	**0**	**1 ± 3 days**	**4, 8[d], 12, 16[d], 20, 24 ± 3 days**	**30, 36, 42, 48 ± 3 days**	**52 ± 3 days**	**53[f]**		**4 Weeks After Last Dose (± 3 days)**
STUDY ENTRY AND GENERAL ASSESSMENTS									
Main Informed Consent	X	-	-	-	-	-	-	-	-
[redacted]									
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-
Complete Medical History	X	-	-	-	-	-	-	-	-
FibroScan[b]	X	-	-	-	-	-	-	-	-
Prior/ Concomitant Medication Evaluation	Continuous starting after the informed consent form is signed through 28 days after end of treatment								
Prior/Concomitant Procedures Evaluation	Continuous starting after the informed consent form is signed through 28 days after end of treatment								
Hemoglobin A1c	X	-	-	-	-	-	-	-	-
Urine EtG Test	X	-	-	Week 24	-	X	-	-	-

Table 3: Table of Events (Continued)

Year 1 - For all subjects

	Screening Phase	Double-Blind, Placebo-controlled Treatment Phase						Early Termination	Post-Treatment Observational Follow-up Phase
Visit Number	**Screening**	**2 Baseline**	**3**	**4-9 Every 4 weeks**	**10-13 Every 6 weeks**	**14**	**15**	**ET[a]**	**28**
Week	**-10 to 0**	**0**	**1 ± 3 days**	**4, 8[d], 12, 16[d], 20, 24 ± 3 days**	**30, 36, 42, 48 ± 3 days**	**52 ± 3 days**	**53[f]**		**4 Weeks After Last Dose (± 3 days)**
Postmenopausal testing: estradiol and follicle-stimulating hormone (for women 50-55 years with undocumented status)	X	-	-	-	-	-	-	-	-
α-fetoprotein	X	-	-	-	-	-	-	-	-
QuantiFERON® -TB Gold Test[c], Hepatitis B & C and HIV Tests	X	-	-	-	-	-	-	-	-
SAFETY ASSESSMENTS									
Adverse Event Evaluation	Continuous starting after the informed consent form is signed through 28 days after end of treatment.								
Complete Physical Examination	X	-	-	-	-	X	-	X	X
Targeted Physical Examination	-	X	X	X	X	-	X	-	-
Vital Signs and Weight	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-
12-Lead ECG	X	-	-	Weeks 4, 12, 24	-	X	-	X	X
Hematology Panel	X	X	X	X	X	X	X	X	X
Chemistry Panel	X	X	X	X	X	X	X	X	X
PT and INR	X	X	X	X	X	X	-	X	X

Table 3: Table of Events (Continued)

Year 1 - For all subjects

	Screening Phase	Double-Blind, Placebo-controlled Treatment Phase						Early Termination	Post-Treatment Observational Follow-up Phase
Visit Number	**Screening**	**2 Baseline**	**3**	**4-9 Every 4 weeks**	**10-13 Every 6 weeks**	**14**	**15**	**ET[a]**	**28**
Week	**-10 to 0**	**0**	**1 ± 3 days**	**4, 8[d], 12, 16[d], 20, 24 ± 3 days**	**30, 36, 42, 48 ± 3 days**	**52 ± 3 days**	**53[f]**		**4 Weeks After Last Dose (± 3 days)**
Urinalysis	X	X	-	X	Week 36	X	-	X	X
Urine cytology	X	-	-	Weeks 12, 24	-	X	-	X	X
FOBT	X	-	-	Weeks 12, 24	Weeks 36, 48	-	-	X	X
Serum β-hCG	X	X	-	X	X	X	-	X	X
Urine β-hCG	-	X[e]	-	Weeks 8, 16	-	-	-	-	-
Pregnancy counseling for FCBP	X	X	X	X	X	X	X	X	X
EFFICACY ASSESSMENTS									
Liver biopsy/histology[f]	X[f]	-	-	-	-	-	X[f]	X[f]	-
[redacted]									

Table 3: Table of Events (Continued)

Year 1 - For all subjects

	Screening Phase	Double-Blind, Placebo-controlled Treatment Phase						Early Termination	Post-Treatment Observational Follow-up Phase
Visit Number	**Screening**	**2 Baseline**	**3**	**4-9 Every 4 weeks**	**10-13 Every 6 weeks**	**14**	**15**	**ET[a]**	**28**
Week	**-10 to 0**	**0**	**1 ± 3 days**	**4, 8[d], 12, 16[d], 20, 24 ± 3 days**	**30, 36, 42, 48 ± 3 days**	**52 ± 3 days**	**53[f]**		**4 Weeks After Last Dose (± 3 days)**
PHARMACOKINETIC [redacted] ASSESSMENTS									
[redacted]									
Blood sample for metabolic tests [redacted]	-	X	-	Week 24	-	X	-	X	-
[redacted]									
INVESTIGATIONAL PRODUCT (IP)									
Dispense IP	-	X[j]	X	X	X	-	-	-	-
Return and Count IP	-	-	X	X	X	X	-	X	-

Table 3: Table of Events (Continued)

Year 2 - For subjects who participate in the active treatment phase:

	Double-Blind, Active Treatment / Extension Phase				Early Termination	Post-Treatment Observational Follow-up Phase
Visit Number	**16**	**17-22 Every 4 weeks**	**23-26 Every 6 weeks**	**27 EOT**	**ET[a]**	**28**
Week	**54[f]**	**55, 58, 62, 66, 70, 74 ± 3 days**	**78, 84, 90, 96 ± 3 days**	**102 ± 3 days**		**4 Weeks After Last Dose (± 3 days)**
	SAFETY ASSESSMENTS					
Prior/ Concomitant Medication Evaluation	Continuous starting after the informed consent form is signed through 28 days after end of treatment					
Prior/Concomitant Procedures Evaluation	Continuous starting after the informed consent form is signed through 28 days after end of treatment					
Adverse Event Evaluation	Continuous starting after the informed consent form is signed through 28 days after end of treatment.					
Complete Physical Examination	-	-	-	X	X	X
Targeted Physical Examination	X	X	X	-	-	-
Vital Signs and Weight	X	X	X	X	X	X
12-Lead ECG	-	Weeks 58, 66, 74	Week 84	X	X	X
Hematology Panel	-	X	X	X	X	X
Chemistry Panel	-	X	X	X	X	X
PT and INR	-	X	X	X	X	X
Urinalysis	-	X	Week 84	X	X	X
Urine cytology	-	Weeks 66, 74	-	X	X	X
FOBT	-	Weeks 62, 74	Weeks 84, 96	X	X	X
Serum β-hCG	X	X (except Week 55)	X	X	X	X
Pregnancy counseling for FCBP	X	X	X	X	X	X

Table 3: Table of Events (Continued)

Year 2 - For subjects who participate in the active treatment phase:

	Double-Blind, Active Treatment / Extension Phase				Early Termination	Post-Treatment Observational Follow-up Phase
Visit Number	**16**	**17-22 Every 4 weeks**	**23-26 Every 6 weeks**	**27 EOT**	**ET[a]**	**28**
Week	**54[f]**	**55, 58, 62, 66, 70, 74 ± 3 days**	**78, 84, 90, 96 ± 3 days**	**102 ± 3 days**		**4 Weeks After Last Dose (± 3 days)**
[redacted]						
PHARMACOKINETIC [redacted] ASSESSMENTS						
[redacted]						
Blood sample for metabolic tests [redacted]	-	-	-	X	X	-
[redacted]						
INVESTIGATIONAL PRODUCT (IP)						
Dispense IP	X	X	X	-	-	-
Return and Count IP	-	X	X	X	X	-

Abbreviations: β- hCG = beta human chorionic gonadotropin; [redacted] ECG = electrocardiogram; [redacted] EtG = ethyl glucuronide; EOT = end of treatment; ET = Early Termination Visit; FCBP = females of child bearing potential; FOBT = fecal occult blood test; HCC = hepatocellular cancer; HIV = human immunodeficiency virus; [redacted] INR = international normalized ratio; IP = investigational product; [redacted] PT = prothrombin time; [redacted] TB = tuberculosis.

[a] Subjects who discontinue the study prior to the Week 52 Visit (subjects who do not participate in the active treatment phase) or the Week 102 Visit (subjects who participate in the active treatment phase) will have an ET Visit. Subjects who discontinue the study prior to the Week 52 will undergo all of the assessments required at the Week 52 Visit and Subjects who discontinue the study after the Week 52 and prior to Week 102 Visit will undergo all of the assessments required at the Week 102 Visit.

[b] FibroScan can be used to determine eligibility for liver biopsy.

[c] 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, 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.

[d] Visit 5 Week 8 and Visit 7 Week 16 will be remote visits. Central laboratory tests, target physical examination, vital sign and weight will not be performed during these remote visits. However, if laboratory tests and/or physical examination is needed based on the Investigator's clinical judgement, an unscheduled visit should be performed at the investigational site. Urine pregnancy test kits will be provided to the subjects at Visit 4 Week 4 and Visit 6 Week 12. At Visit 5 Week 8 and Visit 7 Week 16 subjects will perform urine β-hCG test at home. IP will be dispensed at Visit 4/Week 4 and Visit 6/Week 12 for these 2 visits.

[e] Urine pregnancy test will be performed to assess subject eligibility prior to the first administration of IP if a serum pregnancy test was not obtained within 72 hours prior to dosing (negative results required for IP administration).

[f] Subjects who do not have a historical biopsy will undergo a liver biopsy procedure for study eligibility. The independent histopathologists will review the liver biopsy specimens to assess whether the subject meets the histological inclusion criteria. Screening liver biopsy will serve as the Baseline assessment. Subjects who discontinue after Week 20 and before Week 52 will undergo a liver biopsy procedure at ET Visit. IP should be stopped 7-10 days prior to Week 53 or ET Visit biopsy and restarted 7 days after biopsy at Week 54 if subjects participate in the active treatment phase.

[redacted]

[j] First dose of IP should be administered at the investigative site.

6. PROCEDURES

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

6.1. Screening Phase

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 10 weeks prior to the first dose of IP (study randomization) unless noted otherwise below.

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

Safety laboratory analyses and all assessments will be performed centrally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

During screening, the following will be performed as specified in Table 3, Table of Events, after informed consent has been obtained:

- Inclusion/exclusion criteria: Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study.
- Demographics: Including age, sex, and race and ethnicity-if allowed by local regulations
- Disease history: Including specific information regarding diagnosis, staging, histology
- Complete medical history: All relevant medical conditions diagnosed/ occurring prior to screening should also be included.
- Prior procedures: Including any prior procedures
- Prior and concomitant medication evaluation: Including all medications (prescription and nonprescription, including vitamins) taken by the subject up to 30 days prior to the 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 at any time, such as previous treatment for tuberculosis or relevant diseases, should also be recorded.
- Complete physical examination (Section 6.5.1)
- Vital Signs, height and weight: Vital signs, including seated blood pressure, body temperature, and heart rate will be taken. Height and weight (to be done in street clothes, no shoes) will also be measured and recorded.
- 12-lead electrocardiogram (ECG) (Section 6.5.2)

- Clinical laboratory evaluations: Clinical laboratory evaluations will be performed by a central laboratory to include the following laboratory assessments below. Subject eligibility and clinical laboratory criteria are provided in Section 4.2. One laboratory re-test is allowed after obtaining Medical Monitor approval if the result is exclusionary during the Screening Period. In subjects with abnormal screening ALP or TBL, another measurement should be obtained at least 4 weeks apart. In subjects with screening AST or ALT, greater than 3 X ULN, another measurement should be obtained at least 4 weeks apart. The subject will be eligible for the study if elevated screening AST, ALT, ALP or TBL values do not increase more than 20%. Subjects with evidence of worsening liver function at baseline are not eligible for the study. In subjects with abnormal screening ALP or TBL or screening AST or ALT, greater than 3 X ULN, baseline values should be established by at least two measurements of AST, ALT, ALP or TBL obtained at least 4 weeks apart. Details pertaining to the central laboratory assessments and panels are included in Section 6.5.3.
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Urinalysis and urine cytology
  - QuantiFERON-TB GOLD (Refer to Section 6.5.3)
  - Hepatitis B and C tests
  - Human immunodeficiency virus (HIV) test
  - Pregnancy test (Serum β-hCG)
  - Postmenopausal tests
  - Urine EtG test
  - α-fetoprotein
  - Fecal occult blood test (FOBT)
- Hemoglobin A1c
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted
- Vibration controlled transient elastography (VCTE)/ FibroScan: Subjects who do not have pathological specimens from a prior liver biopsy obtained within 6 months of Screening and available for central reading are suggested to have results from non-invasive tests available to help determine eligibility for liver biopsy during Screening. In most subjects, these tests are Fibrosis-4 (FIB-4) and VCTE by FibroScan®. Availability of FIB-4 and VCTE, or other tests [redacted] obtained within 3 months of Screening may be acceptable. Other subjects may undergo sequential FIB-4 determination and VCTE by FibroScan during Screening to help assess the likelihood of having Stage 2 or Stage 3 fibrosis based on Investigator's clinical judgement.

Vibration controlled transient elastography should be performed with the subjects in a fasting condition for 2 hours before the procedure, lying in supine position with normal breathing, and with the right arm in maximum abduction to allow optimal exposure of the right lateral abdomen.

- Liver biopsy (Section 6.6.1)

  Screening liver biopsy will be performed in subjects who do not have pathological specimens from a prior liver biopsy obtained within 6 months of Screening and available for central reading.

[redacted]

- Adverse Event: 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. Refer to Section 10 for details pertaining to AEs.

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. For all subsequent visits, an administrative window of ± 3 days is permitted except Visit 15/Week 53 and Visit 16/Week 54 (for the subjects who participate in the active treatment phase). Visit 15/Week 53 should be performed 7 to 10 days after Visit 14/Week 52 and Visit 16/Week 54 (for the subjects who participate in the active treatment phase) should be performed 7 to 10 days after Visit 15/Week 53. Scheduling of Visits 3 to 14 is based on Visit 2/Week 0 (randomization date) and scheduling of Visits 17 to 27 (for the subjects who participate in the active treatment phase) is based on Visit 16/Week 54 (re-randomization date). [redacted]

Visit 5 Week 8 and Visit 7 Week 16 will be remote visits. Assessments performed at these visits have been specified in the Table of Events, Table 3

The following evaluations will be performed at the frequency specified in the Table of Events, Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Adverse event evaluation (continuously)
- Concomitant medications evaluation (continuously)
- Concomitant procedures evaluation (continuously)
- Counseling about pregnancy precautions and the potential risks of fetal exposure
- Complete physical examination (Section 6.5.1)
- Targeted physical examination (Section 6.5.1)
- Vital signs and weight (Section 6.1)

- 12-lead ECG (Section 6.5.2)
- Clinical Laboratory Evaluations (Section 6.5.3):
  - Hematology panel
  - Coagulation tests
  - Chemistry panel
  - Urinalysis and urine cytology
  - Serum pregnancy test
  - Urine pregnancy test at Visit 5 Week 8 and Visit 7 Week 16
  - Urine EtG test
  - Fecal occult blood test (FOBT)
- Efficacy assessment (Section 6.6):
  - Liver biopsy/histology

- Investigational product (IP) dispensation: The Principal Investigator, Sub-investigator, or Study Coordinator should make an effort to witness subjects taking their first dose and record the date and time in the source document record. Subjects are instructed to take 3 tablets of IP QD, approximately the same time of day (preferably in the morning), with or without food. Visit 5/Week 8 and Visit 7/Week 16 will be remote visits and IP will be dispensed at Visit 4/Week 4 and Visit 6/Week 12 for these 2 visits.
- Investigational product (IP) return (all used and unused blister cards) and IP compliance assessment (Section 7.6)

6.2.1. Unscheduled Visits

Unscheduled visits, if needed, may occur at any time, in particular for safety reasons (or efficacy reasons) as deemed necessary by the Investigator or site staff, or for any reason that the subject must return to study center as it pertains to the study (eg, to pick up additional or replacement IP). The Unscheduled Visit eCRF will be made available to the site staff, in order to record the necessary unscheduled assessments and/or procedures.

6.3. Early Termination

An early termination (ET) 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 3:

- Adverse event evaluation
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Counseling about pregnancy precautions and the potential risks of fetal exposure
- Complete physical examination (Section 6.5.1)
- Vital signs and weight (Section 6.1)
- 12-lead ECG (Section 6.5.2)
- Clinical Laboratory Evaluations (Section 6.5.3):
  - Hematology panel
  - Coagulation tests
  - Chemistry panel
  - Urinalysis and urine cytology
  - Serum pregnancy test
  - Fecal occult blood test (FOBT)
- Efficacy assessment (Section 6.6):
  - Liver biopsy/histology

[redacted]

[redacted]

- Investigational product (IP) return (all used and unused blister cards) and IP compliance assessment (Section 7.6)

6.4. 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.

- Adverse event evaluation
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Counseling about pregnancy precautions and the potential risks of fetal exposure
- Complete physical examination (Section 6.5.1)
- Vital signs and weight (Section 6.1)
- 12-lead ECG (Section 6.5.2)
- Clinical Laboratory Evaluations (Section 6.5.3):
  - Hematology panel
  - Coagulation tests
  - Chemistry panel
  - Urinalysis and urine cytology
  - Serum pregnancy test
  - Fecal occult blood test (FOBT)

6.5. Safety Assessments

6.5.1. Physical Examination

Complete physical examinations will include evaluation of the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. Gynecological, urogenital, and rectal examinations will not be performed unless needed.

A targeted physical examination includes evaluation of the respiratory, cardiovascular, abdominal systems. Gynecological, urogenital and rectal examinations will not be done unless needed.

Results of the physical examination will be recorded only in the source documents. Clinically significant abnormal findings (with the exception of the disease under study [NASH]) identified prior to first dose of IP will be recorded on the eCRF as medical history; clinically significant findings after the first dose of IP will be recorded as AEs.

6.5.2. Electrocardiogram

Subjects will have a 12-lead electrocardiogram (ECG) at the frequency specified in Table 3. The investigator or designee will use his/her own ECG equipment. The same ECG equipment should be used throughout the entire study. A standard 12-lead ECG (reporting PR interval, QRS, QT and corrected QT [QTc] intervals) will be performed by the Investigator or qualified designee. For safety evaluation of the subject's ECG, the Investigator should utilize the QT correction method (Fridericia). ECGs will be performed after the subject has been in the supine or near supine position for at least 10 minutes.

An ECG tracing from each prespecified visit will be reviewed by the Investigator or medically-qualified designee and any abnormal results will be classified as clinically significant (CS) or not clinically significant (NCS) for real-time safety monitoring. Any CS abnormal ECG result should be reported as an AE and followed to resolution (ie, until it returns to baseline, stabilizes, or becomes NCS as judged by the Investigator or medically-qualified designee).

6.5.3. Clinical Laboratory Assessments

Clinical laboratory evaluations will be performed by a central laboratory to include the following laboratory assessments performed at the frequency specified in Table 3. Clinical laboratory evaluations are required to be fasting at Baseline Visit, Week 24 Visit, and Week 52 Visit/ Week 102 Visit (as applicable) or at the Early Termination Visit if subjects discontinue from the study prior Week 52 Visit/ Week 102 Visit (as applicable). "Abnormal, clinically significant" results should be recorded in the Medical History eCRF if found prior to first dose of IP, or in the AE eCRF if found after the first dose of IP.

- 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, white blood cell (WBC) count (with differential), neutrophil count (percent and absolute), and platelet count.
- Coagulation tests: including prothrombin time (PT) and INR.
- Chemistry Panel: including total protein, albumin, calcium, phosphorous, glucose, lipid panel (total cholesterol, HDL, LDL, and triglycerides), uric acid, TBL, ALP, AST/ serum glutamic oxaloacetic transaminase (SGOT), ALT/ serum glutamic pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, and lactic dehydrogenase (LDH).
- Urinalysis: including dipstick urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen). Microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the dipstick urinalysis is abnormal.

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

Note: A positive QuantiFERONTB 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, 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.

- Hepatitis B and hepatitis C testing: testing will be performed at Screening. The hepatitis screen includes testing for hepatitis B surface antigen (HBsAg) and antibody, hepatitis B core antibodies (IgG/IgM), and hepatitis C antibodies (HCV Ab). A positive result for one or more hepatitis B tests will disqualify the subject from further participation in the study (See Appendix D). A subject who is HCV Ab positive must be excluded unless the subject has a history of HCV and sustained viral response (undetectable HCV RNA) for at least 2 years prior to Screening or historical biopsy including negative HCV RNA at Screening. 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.

- Human immunodeficiency virus test: testing will be performed at Screening.
- Hemoglobin A1c: test will be performed at Screening.
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed.

  Urine pregnancy test will be performed to assess subject eligibility within 72 hours 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).

- Postmenopausal test: Estradiol and follicle-stimulating hormone (FSH) levels are required for all females 50 to 55 years of age who do not have documentation confirming their postmenopausal status. Postmenopausal test will be performed at Screening.
- Urine EtG test: Test will be performed as indicated in Table 3.
- Fecal occult blood test (FOBT): test will be performed as indicated in Table 3.

6.5.4. Action Plan for Monitoring Potential Hepatotoxicity

The evaluation of liver safety signals in clinical trials that enroll individuals with pre-existing liver disease presents special challenges. Refer to Appendix C for the specific guidelines for monitoring and interrupting and discontinuing subjects based upon elevations in the liver function tests after treatment with IP.

Treatment arm safety stopping rules will be finalized in consultation with members of the DMC based on the:

- Marked elevations of aminotransferases to 5 times, 10 times, or 20 times the baseline values in the active treatment and not observed or less frequent in the placebo group.
- One or more Hy's law cases, as defined by the following preliminary parameters, based on Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation; (FDA, 2009) and modified as suggested by criteria to account for patients with pre-existing liver injury (Parks, 2013).

6.6. Efficacy Assessment

6.6.1. Histological Scoring System for NAFLD

Liver biopsy has been widely considered as the "gold standard" for assessing fibrosis in NASH and has been validated in a large cohort of NASH patients (Kleiner, 2005). Liver biopsy will be performed during Screening period and Week 53 visit as described in Table 3, Table of Events. Subjects who discontinue after Week 20 and before Week 52 will undergo a liver biopsy procedure at ET Visit. Investigational product should be stopped 7 to 10 days prior to biopsy and restarted 7 days after biopsy. Refer to operational manual for the biopsy collection.

Screening liver biopsy will be performed in subjects who do not have pathological specimens from a prior liver biopsy obtained within 6 months of Screening and available for central reading.

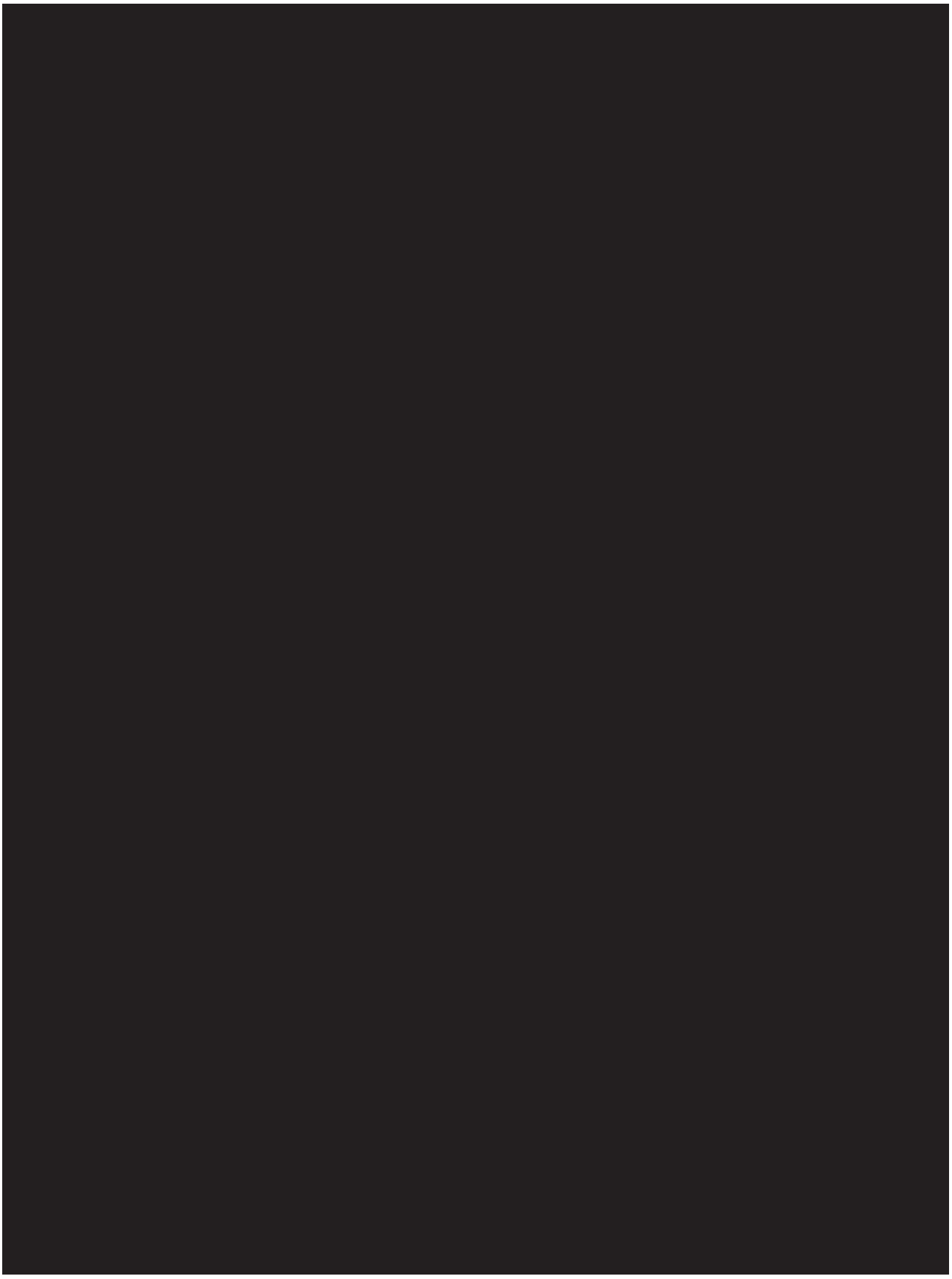
The historical biopsy within 6 months of Screening and liver biopsy collected during the study will be assessed in a blinded fashion by a central pathologist with extensive experience in assessing treatment response in NASH clinical trials.

Biopsy specimens will be graded according to NASH CRN Histologic Scoring System. The scoring system comprised: steatosis (on a scale of 0 to 3), lobular inflammation (on a scale of 0 to 2), hepatocellular ballooning (on a scale of 0 to 2), and fibrosis (on a scale of 0 to 4) (Kleiner, 2005).

Liver fibrosis stage ranges from Stage 0 to Stage 4. Stage 0 is defined as none; Stage 1 is defined as perisinusoidal / periportal fibrosis; focally or extensively present; Stage 2 is defined as perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis; Stage 3 is perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis; Stage 4 is defined as cirrhosis (Brunt, 1999). Improvement in liver fibrosis, defined as a reduction of ≥1 stage, will be assessed according the NASH CRN Histologic Scoring System.

Non-alcoholic fatty liver disease activity score (NAS) includes the features of injury that are potentially reversible in the short term. The score is defined as steatosis (0 to 3), lobular inflammation (0 to 3) and hepatocellular ballooning (0 to 2) with a total score ranging from 0 to 8 and the higher scores indicating increasing disease activity.

[redacted]



[redacted]

6.8. Biomarkers [redacted]

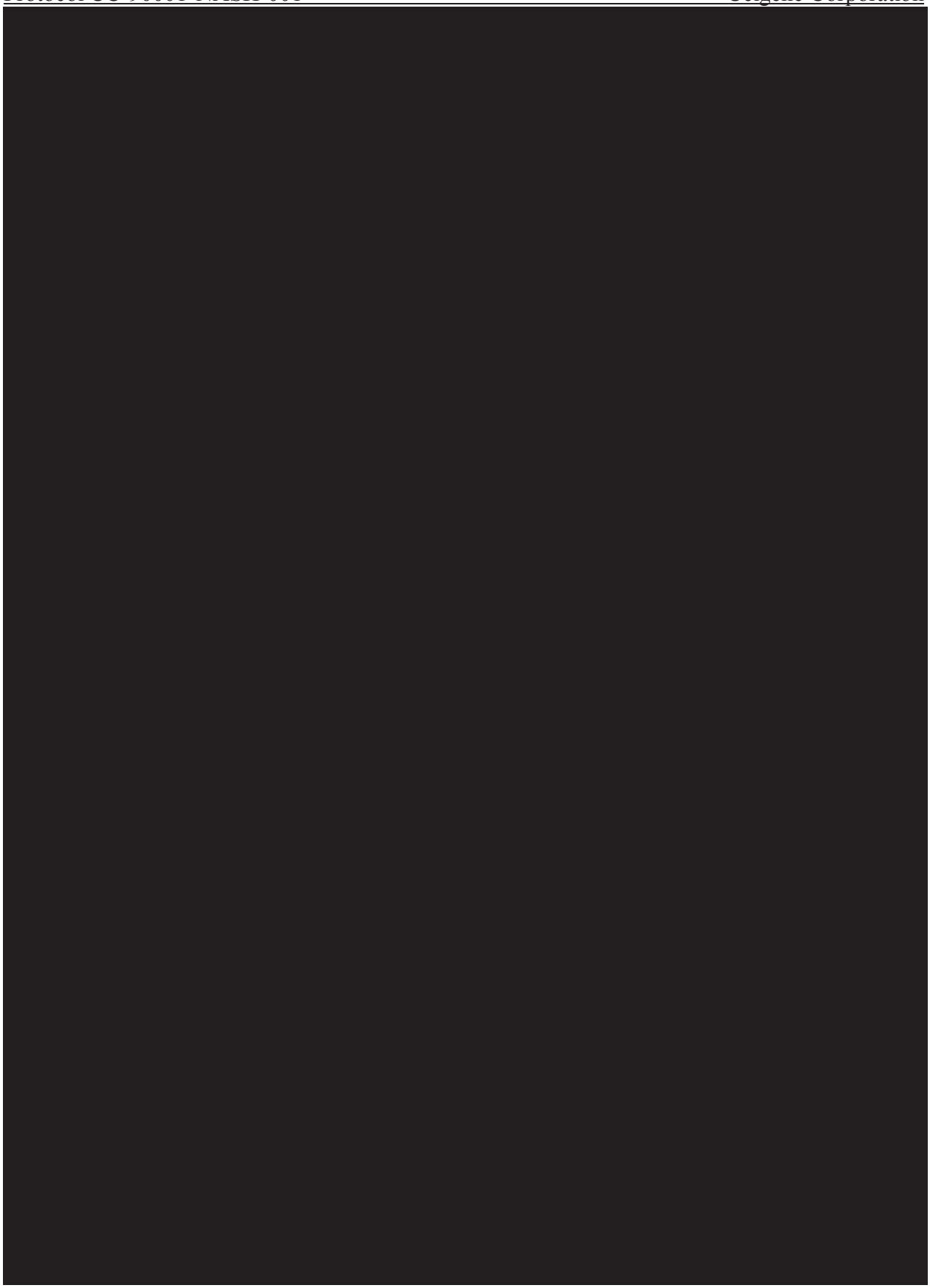
6.8.1. Biomarkers [redacted]

[redacted]

- Metabolic parameters

  [redacted]

  - Serum lipids (total cholesterol, LDL, HDL, and triglycerides)



7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

CC-90001, film-coated 100 mg and 200 mg tablets and placebo tablets matching the appearance of 100 mg and 200 mg tablets, will be supplied by the Sponsor and will be labeled appropriately as IP for this study.

All CC-90001 IP will be packaged in a double-blinded fashion and dispensed to subjects in the form of blister cards. All placebo tablets will be identical in appearance to active study IP. The dosing schedule is described in Section 7.2.

7.2. Treatment Administration and Schedule

Subjects are instructed to take 3 tablets once daily, approximately the same time of day (preferably in the morning), with or without food.

- **52-Week Double-blind Placebo-controlled Treatment Phase: Baseline (Visit 2) to Week 52 (Visit 14):**

  Subject will receive 3 tablets once daily as follows:

  - CC-90001 100 mg (one 100 mg tablet), and placebo (two 200 mg placebo tablets) (only for subjects who are randomized prior to implementation of Protocol Amendment 4)
  - CC-90001 200 mg (one 200 mg tablet), and placebo (one 100 mg placebo tablet and one 200 mg placebo tablet)
  - CC-90001 400 mg (two 200 mg tablets), and placebo (one 100 mg placebo)
  - Placebo (one 100 mg placebo tablet and two 200 mg placebo tablets)

- **50-Week Double-blind Active Treatment Phase (for subjects who participate in the active treatment phase):**

  During the 50-week double-blind active/extension treatment phase subjects who were initially randomized to active treatment arms will remain in their assigned dose groups. Subjects who were initially randomized to placebo arm will 200 mg QD or 400 mg QD. The subjects who were previously re-randomized to the 100 mg dose group prior to implementation of Protocol Amendment 4 will remain in the 100 mg dose group.

Blinded IP will be packaged in accordance with all required guidelines and in a manner that supports the study design and visit schedule defined within Section 5.

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 be subject to the overdose definition it must be both required and an IP. In this study, the only required IP is CC-90001 or placebo; hence, the overdose definition applies only to CC-90001 or matching placebo. Other medications (eg, concomitant medications, include those for treatment of AEs) are excluded from a designation of overdose.

Overdose for this protocol is defined as ingestion of > 3 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 eCRF 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 eCRF page.

7.2.2. Dose Interruptions

This is a dose-finding study, therefore no dose reductions will be permitted. However, in the event a subject experiences a study drug-related adverse event, a temporary IP interruption for up to 4 days will be permitted at any time 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 a 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 discontinued from the study IP and enter into the Post-treatment Observational Follow-up Phase.

[redacted] The subjects should interrupt IP 7 to 10 days prior to an elective surgical procedure and restart 7 days after any surgical procedures, including liver biopsy.

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.

7.3. Method of Treatment Assignment

Approximately 180 adult male and female subjects with a confirmed diagnosis of NASH and Stage 2 or Stage 3 fibrosis will be randomized 1:1:1 to treatment with oral CC-90001 (200 mg QD, 60 subjects; 400 mg QD, 60 subjects) or matching placebo (60 subjects) for 52 weeks. Randomization will be stratified by liver fibrosis stage (Stage 2/Stage 3) and by the presence of Type 2 DM (yes/no). To ensure enrollment of a suitable number of subjects with Stage 3 fibrosis, up to 15 subjects with Stage 2 fibrosis may be enrolled per arm. Randomization, treatment assignment and stratification will be managed by an IWRS. Prior to the implementation of Protocol Amendment 4, subjects were also randomized into a 100 mg QD dose group. The subjects who were previously randomized to the 100 mg dose group will remain in the 100 mg dose group throughout the study. It is expected that approximately 10-15 subjects will have been randomized to the 100 mg group at time of implementation of Protocol Amendment 4. Thus, a total of approximately 195 subjects will participate in the study.

The DMC will be responsible for review of the interim analyses data and will make recommendations to the Sponsor, who will be responsible for final decision-making. An unblinded interim analysis will be performed after approximately 50% of subjects with Stage 2 or Stage 3 fibrosis complete 52 weeks of placebo-controlled treatment phase (as described in the DMC Charter). A decision may be made to stop enrolling a treatment arm due to futility if not fully enrolled at interim analysis.

Subjects who sign ICF prior to the implementation of Protocol Amendment 4, will have an option to participate in a double-blind active treatment phase. At Week 54, all placebo subjects will be re-randomized 1:1 by IWRS to the 200 mg QD or 400 mg QD dose groups. Prior to the implementation of Protocol Amendment 4, subjects were also re-randomized into a 100 mg QD dose group. The subjects who were previously re-randomized to the 100 mg dose group will remain in the 100 mg dose group. Subjects who were initially randomized to active treatment arms will remain in their assigned dose groups through the end of the double-blind active treatment phase.

Subjects who sign ICF after the implementation of Protocol Amendment 4 will receive treatment in a double-blind placebo-controlled treatment phase only.

Designated study personnel at the investigational sites will be assigned password-protected, coded identification numbers, which give them authorization to access the IWRS to randomize subjects. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the IWRS will assign a randomization identification number. Confirmation of the randomization will be sent via fax to the investigational site, Celgene and/or its representative.

During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization number assigned by the IWRS.

7.4. Packaging and Labeling

The label(s) for IP will include 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.

7.5. 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).

7.6. 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 case report form (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 3. 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 a 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 discontinued from the study, and enter into the Follow-up Period.

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 $\leq 120\%$, $> 120\%$.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression.

All medications (prescription and non-prescription), treatments, and therapies taken by the subject from screening throughout their 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 eCRF. The dose, unit, frequency, route, indication, date the medication was started, and date the medication was stopped (if not ongoing) must be recorded.

[redacted]

8.1. Permitted Concomitant Medications and Procedures

[redacted]

- The following drugs may be used during the trial, but doses must have been stable for 3 months prior to Screening or historical biopsy used for Screening assessment and the subject agrees to maintain stable doses during the course of the study, unless required to adjust doses due to safety reasons: ursodeoxycholic acid, gemfibrozil, metformin, sodium-glucose co-transporter 2 (SGLT2) inhibitors (eg, canagliflozin), dipeptidyl peptidase-4 inhibitors ("gliptins") (such as sitagliptin), glucagon peptide-1 agonists (eg, liraglutide), anti-obesity medications (eg, orlistat, lorcaserin, liraglutide, phentermine-topiramate, or naltrexone-bupropion). If SGLT2 inhibitors, GLP-1 agonists and anti-obesity have been recently discontinued, the treatment must have been stopped for at least 3 months prior to Screening or historical biopsy.
- Thiazolidinediones (eg, pioglitazone) and vitamin E are allowed during the study, but doses must have been stable for 3 months prior to Screening or 3 months prior to historical biopsy used for Screening assessment and the subject agrees to maintain stable doses during the course of the study. If thiazolidinediones (eg, pioglitazone) or vitamin E have been recently discontinued, the treatment must have been stopped for at least 3 months prior to Screening or historical biopsy.

Exceptions may be made to initiation or changing doses of these medications if, in the opinion of the Investigator, a different dose of such medication(s) are needed to support best medical practice in the time frame of study participation AND the new dose will not interfere with subject safety or the interpretation of study results. In such instances, the Sponsor's Medical Monitor and Investigator must concur.

8.2. Prohibited Concomitant Medications and Procedures

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

- Drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) for the duration of the study
- Vitamin E for treatment of NASH cannot be initiated after Screening.
- Biologic agents (eg, TNF inhibitors), or cytokine inhibitors (eg, tofacitinib) within 3 months of Screening.
- 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 an approved agent for treatment of NASH within 6 months prior to Screening or historical biopsy.
- Use of cannabinoid products other than cannabis oils during the study
- Use of live attenuated or investigational SARS-CoV-2 vaccine

Exceptions may be made to use of these medications if, in the opinion of the Investigator, the medication is needed to treat an unrelated medical condition (eg, a brief course of systemic corticosteroids for an asthma exacerbation) 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. Required Concomitant Medications and Procedures

Other than medications required for local anesthesia related to liver biopsy, there are no required concomitant medications.

Required procedures include liver biopsy.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 2, multicenter, multinational, double-blind, randomized, placebo-controlled, dose-finding study evaluating the efficacy, safety, PK, [redacted] of treatment with CC-90001, compared with placebo, in NASH subjects with either Stage 2, or Stage 3 fibrosis.

The objective of the statistical analysis is to evaluate the efficacy and safety of CC-90001 versus placebo for 52 weeks in subjects with NASH and Stage 2, or Stage 3 fibrosis.

The primary analysis will be performed after all subjects have completed the Placebo-controlled Phase (Weeks 0 to 52). The final analysis will be performed at the study completion, ie, when all subjects have completed the Observational Follow-up Phase. To maintain the blind at the site and subject level, the individual subject treatment assignments will not be revealed to the investigators until after the final database lock following the study completion.

This section outlines the statistical analysis strategy and details will be documented in a separate Statistical Analysis Plan (SAP).

9.2. Study Population Definitions

The Full Analysis Set (FAS) population will consist of all subjects who are randomized and received at least one dose of IP. Subjects will be included in the treatment group to which they are randomized.

The safety population will consist of all subjects who are randomized and received at least one dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually receive.

The per protocol (PP) population will consist of all subjects included in the FAS population who receive at least one dose of IP, have both baseline and post-treatment liver fibrosis score evaluation, and have no important protocol deviations which may affect analyses in the Placebo-controlled Phase. Subjects will be included in the treatment group to which they are randomized.

9.3. Sample Size and Power Considerations

The estimated improvement on ≥1 fibrosis score in Stage 3 subjects of 45% for CC-90001 group and 20% for the placebo group is based on a Phase 2 study of selonsertib, which reported a 23% treatment difference (43% in the selonsertib 18 mg group versus 20% in the simtuzumab group-a compound that was not demonstrated to be effective for NASH with a treatment response similar to placebo from other clinical trials) (Loomba, 2018; Neuschwander-Tetri, 2015).

With the above assumed treatment responses for the primary endpoint between the highest CC-90001 dose group and the placebo, and further assuming a similar treatment effect in Stage 2 subjects, the sample size of 60 for the placebo, 200 mg, and 400 mg treatment group and an expected sample size of 10-15 for the 100 mg treatment group provides the ability to determine a dose response with 80% power, and 5% type I error rate.

This sample size was estimated using the multiple comparison and dose-response modeling (MCP-Mod) procedure and considering five dose-response models (linear, log-linear, two Emax shapes and logistic) (Bretz, 2005; R-package "MCPMod", version 1.0-10.1 August 5, 2017).

Determination of the minimum effective dose (MED) will follow the MCP-Mod method (Bretz, 2005). Based on this method, a dose will be considered as MED if it satisfies the following two criteria: (i) the response rate of the dose is greater than that of placebo by a clinically relevant treatment difference (Δ), and (ii) the lower confidence bound of the response rate of that dose has to be greater than that of placebo. Simulations were run to assess the sensitivity to determine the MED with examples of Δ and 80% confidence intervals of the response rates.

Table 5: Probability of Each Dose to Be Considered the MED for Various Response Scenarios and Delta

	Response Rate			MED Probability[c]		
Scenarios	**100 mg**	**200 mg**	**400 mg**	**Dose (mg)**	**Δ=0.10**	**Δ=0.15**
1[b]	0.325 (50% of emax[c])	0.45	0.45	100	52.80%	44.18%
				200	37.06%	39.84%
				400	0.44%	6.30%
				MED not identified	9.70%	9.68%
2	0.2625 (25% of emax)	0.3875 (75% of emax)	0.45	100	30.38%	20.06%
				200	55.86%	49.30%
				400	1.54%	18.62%
				MED not identified	12.22%	12.02%
3	0.25 (20% of emax)	0.325 (50% of emax)	0.45	100	17.48%	8.04%
				200	62.06%	39.30%
				400	4.26%	36.96%
				MED not identified	16.20%	15.70%

Abbreviations: PBO = placebo; MED = minimum effective dose.
Response Rate for PBO=0.2
[b] Response rate at the 100 mg dose closer to response rate at the next dose than the other scenarios.
[c] emax is the assumed maximum effect of 45%-20%.
[c] With assumed sample size being 15 subjects for the 100 mg dose group and 60 subjects otherwise.
Δ clinically relevant treatment difference.

Based upon these assessments, the planned sample size provides high sensitivity to determine a MED when a range of response rates and clinically significant effects are assumed. Details of the simulations and estimations will be further elaborated in the Statistical Analysis Plan. In addition to considering MED purely based on efficacy in response rates, the overall determination of the MED will also account for additional efficacy and safety endpoints.

Therefore, approximately 180 subjects will be randomized in a 1:1:1 ratio to receive CC-90001 (200 mg QD, 400 mg QD) or placebo. Randomization will be stratified by liver fibrosis stage (Stage 2/Stage 3) and by the presence of Type 2 DM (yes/no). Approximately 60 subjects with

Stage 2 or Stage 3 fibrosis will be enrolled per arm. To ensure enrollment of a suitable number of subjects with Stage 3 fibrosis, up to 15 subjects with Stage 2 fibrosis may be enrolled per arm. Randomization to one stratum will be halted once the enrollment target is achieved for that stratum.

Subjects who have been randomized to the 100 mg QD treatment arm prior to implementation of Protocol Amendment 4 will be included in the study populations as appropriate. It is expected that randomization into the 100 mg dose group will be stopped at approximately 10-15 randomized subjects at time of implementation of Protocol Amendment 4. Thus, a total of approximately 195 subjects will participate in the study.

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 Medical Dictionary for Drug Regulatory Activities (MedDRA) system organ class and preferred term.

9.5. Subject Disposition

A summary of analysis population allocation will be provided. Subject disposition (entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for the Placebo-controlled Phase (Weeks 0 to 52) and the Active Treatment Extension Phase (Weeks 52 to 102). 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. Efficacy Evaluation for the Placebo-controlled Phase (Weeks 0 to 52)

For the Placebo-controlled Phase (Weeks 0 to 52), the analyses for efficacy endpoints will be based on the FAS. Statistical comparisons will be made between each of CC-90001 treatment groups versus placebo. All statistical tests will be at the two-sided 0.05 significance level and the corresponding p-values and 95% confidence intervals (CIs) will be reported. No adjustment for multiple comparisons will be made in this phase 2 study. The nominal p-values will be reported to give an indication of the strength of association regarding the treatment differences.

9.6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who achieve a ≥1 stage improvement in liver fibrosis using the NASH CRN Histological Scoring System at Week 52. It will be analyzed using the FAS.

The estimand of primary interest is defined in terms of the following four attributes:

A. The population is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population (FAS);

B. The variable is the proportion of subjects who achieve a ≥1 stage improvement in liver fibrosis at Week 52. Missing values due to early termination will be imputed using data

collected at the early termination visit if available; otherwise missing values will be imputed using the non-responder imputation (NRI) method;

C. Potential intercurrent events are captured through the variable definition (B).

D. The summary measure is the difference in response proportions.

With this missing data handling approach, the estimand answers a clinically relevant question that compares the proportion of subjects who achieve the defined response criteria at Week 52 in the FAS.

The primary efficacy endpoint will be analyzed using the Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factors (fibrosis stage (Stage 2 /Stage 3) and by the presence of Type 2 DM (yes/no), at randomization) in order to compare each of CC-90001 treatment groups versus placebo. The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided. A sensitivity analysis will be performed using the PP population.

9.6.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on the FAS. The 2-sided p-values and 2-sided 95% CIs will be reported for treatment difference between each of the CC-90001 treatment groups versus placebo.

The binary endpoints will be summarized using counts and percentages, and the treatment comparison will be performed similarly as the primary endpoint using the CMH test.

The continuous efficacy endpoints will be summarized using mean, standard deviation (SD), median, minimum, maximum, and number of observations analyzed. For all continuous efficacy endpoints, the treatment comparisons will be performed using a mixed model of repeated measures (MMRM) as the primary analysis method of the secondary efficacy endpoints. The MMRM will use the change from baseline as the dependent variable and will include dose, time on treatment, and their interaction as fixed effects covariates. The model will also include the stratification factors (fibrosis stage (Stage 2/ Stage 3) and presence of Type 2 DM (yes/no), at randomization) and corresponding baseline value as fixed effects covariates. Time will be treated as a categorical variable in the MMRM and will be considered as a repeated effect. All post-baseline measurements up to Week 52 will be included in this analysis with no imputation of missing data other than that inherent in the MMRM. Within-group least-squares (LS) means and the associated standard errors (SEs) and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM.

As a sensitivity analysis method for all secondary continuous efficacy endpoints an analysis of covariance (ANCOVA) model will be used. The ANCOVA model will use the change from baseline as the dependent variable, treatment group as a fixed factor, and the baseline value and stratification factors (fibrosis stage (Stage 2 /Stage 3) and presence of Type 2 DM (yes/no), at randomization) as covariates. Within-group least-squares (LS) means and the associated standard errors (SEs) and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the ANCOVA model.

9.6.1.4. Dose-Response modelling

The method for dose-response modeling called MCP-Mod (Section 9.3 and Bretz, 2005) will be applied to the primary endpoint and select additional endpoints. It will allow for an evaluation of which dose-response curves are the best fit given the 52 weeks data and a potentially more accurate estimation of the MED. In this study, MCP-Mod delivers at least 80% power to ascertain a dose response with type I error rate of 5% (c.f. section 9.3). Under the scenarios evaluated, it has high probability to determine the MED. The details will be further elaborated in the Statistical Analysis Plan.

9.6.1.5. Subgroup Analysis

Subgroup analyses for the primary efficacy endpoint based upon baseline demographic (age, gender, race, etc.) or baseline disease characteristics will be provided to determine the robustness of the treatment effect.

9.7. Safety Analysis

The safety analyses will be performed using the safety population, defined as all subjects who are randomized and receive at least one dose of investigational product.

Safety will be assessed by clinical review of all relevant parameters including treatment emergent adverse events (TEAEs), laboratory tests, vital signs, and ECG; no inferential testing for statistical significance will be performed. Data from safety assessments will be summarized descriptively for the Placebo-controlled Phase (Weeks 0 to 52) by the treatment group of CC-

90001 100 mg, 200 mg QD, 400 mg QD, and placebo; and for the CC-90001 Exposure Phase for subjects who receive at least one dose of CC-90001 treatment. For all safety analyses baseline will be relative to the first dose date following randomization at Week 0.

Adverse events will be classified using the MedDRA classification system. All TEAEs will be summarized by system organ class, preferred term, severity and relationship to investigational product. The TEAEs leading to death or to discontinuation from treatment and serious adverse events will be summarized and listed separately.

Data from other safety assessments will be summarized descriptively. Shift tables for laboratory parameters showing the number of subjects with values low, normal, and high comparing with the normal reference ranges pre-treatment versus post treatment will be provided.

9.8. Interim Analysis

An unblinded futility analysis will be performed after approximately 50% of subjects complete 52 weeks of treatment. The DMC will review the totality of the available data to determine the following options:

- Continue the study as planned
- Terminate the study for futility
- Stop enrolling a treatment arm due to futility if not fully enrolled at interim analysis

The details of the interim analysis will be documented in the DMC Charter.

Additional interim analyses may be conducted.

9.9. Other Topics

9.9.2. Internal Safety Management Team

In addition to ongoing safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, SAEs, discontinuations due to AEs, and abnormal laboratory findings will be reviewed internally by the Celgene Safety Management Team (SMT). The review will follow the Council for International Organizations for Medical Sciences, Working Group VI (CIOMS VI) recommendations. The SMT is comprised of lead representatives from multiple Celgene functions engaged in the CC-90001 development

program. The scope, conduct, processes, and accountabilities are specified by Celgene Standard Operating Procedure (SOP).

9.9.3. External Data Monitoring Committee

Safety monitoring will also be performed by an external, independent DMC. A DMC will be convened that will include physician experts with experience in treating subjects with NASH and a statistician, all of whom are not otherwise involved in the study conduct and for whom there is no identified conflict of interest. During the course of the study, the DMC will review the unblinded safety data regularly as well as safety and efficacy data in accordance with the guidelines for the preplanned interim analyses. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the DMC members for each scheduled meeting. Operational details for the DMC will be detailed in the DMC Charter.

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 the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the AE 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, including AEs related to SARS-CoV-2 infection, 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. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs that occur after first dose of IP must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event via Electronic Data Capture (EDC) system.

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.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- 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, the AE screen of the eCRF must be completed and ticked 'serious'.

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.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0);

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

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 at least 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 the AE page/screen of the eCRF, and ticked as 'serious' in EDC. All SAEs that occur after first dose of IP must be reported to Celgene Drug Safety via EDC within 24 hours of the Investigator's knowledge of the event. 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 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 in EDC, but do not require reporting to Celgene Drug Safety.

The SAE report entered into EDC 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 the death certificate are to be provided to Celgene Drug Safety via EDC as soon as these become available. Any follow-up data should be added to the existing SAE case in EDC.

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 through EDC.

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.

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 Pregnancy Report Form Completion Guidelines.

11. DISCONTINUATIONS

11.1. Individual Subject Stopping Criteria and Criteria for Review of Clinical Data by the DMC

11.1.1. Individual Subject Stopping Criteria

The subject will be discontinued from the study:

- If the subject has a positive FOBT at a study visit and a decrease of hemoglobin from baseline by at least 10% at that study visit or subsequent visits before next FOBT is performed
- If the subject develops a Grade 3 or higher drug-related AE by CTCAE Version 5.0 grading system
- If the subject develops a Grade 4 or higher AE by CTCAE Version 5.0 grading system
- If the subject develops decompensated liver disease such as clinically significant ascites, hepatic encephalopathy, or variceal bleeding
- If the subject meets discontinuation criteria outlined in Appendix C

11.1.2. Criteria for Review of Clinical Data by the DMC

The study enrollment will be paused, and the clinical data will be reviewed by the DMC for safety before proceeding with the trial:

- If a subject experiences a Grade 5 AE by CTCAE Version 5.0 grading system, the safety report(s) will be submitted to the FDA for review and discussion prior to dosing any subject
- If 2 subjects develop drug-related Grade 4 AEs by CTCAE Version 5.0 grading system
- If 3 subjects develop the same drug-related Grade 3 AEs by CTCAE Version 5.0 grading system

Treatment arms stopping criteria are described in Section 6.5.4.

11.2. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

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.

11.3. 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
- Other (to be specified on the CRF)

The reason for study discontinuation 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 IWRS by using an emergency unblinding personal identification number (PIN), and the Investigator should call IWRS for unblinded dose information.

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/EC approval but will be submitted to the IRB/EC 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.

Investigational product 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 and entered into the clinical database via electronic CRF per Celgene 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, 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. Product Quality Complaints 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 subject. 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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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADL	Activities of daily life
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
ASK1	Apoptosis signal-regulating kinase 1
[redacted]	[redacted]
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
AUC	Area under the curve
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
AUDIT	Alcohol Use Disorders Identification Test
[redacted]	[redacted]
β-hCG	Beta-subunit of human chorionic gonadotropin
BID	Twice daily
BUN	Blood urea nitrogen
CBC	Complete blood count
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
CIOMS	Council for International Organizations for Medical Sciences, Working Group
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	Maximum plasma concentration of drug
CMH	Cochran–Mantel–Haenszel

APPENDIX A: TABLE OF ABBREVIATIONS (CONTINUED)

Abbreviation or Specialist Term	Explanation
CP	Child-Pugh
CRN	Clinical Research Network
CRF	Case report form
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CVID	Common variable immunodeficiency
[redacted]	[redacted]
[redacted]	[redacted]
DM	Diabetes mellitus
DMC	Data monitoring committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
[redacted]	[redacted]
EtG	Ethyl glucuronide
EOT	End of treatment
ET	Early Termination
FAS	Full Analysis Set
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
FOBT	Fecal occult blood test
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GD	Gestation Day
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
[redacted]	[redacted]

APPENDIX A: TABLE OF ABBREVIATIONS (CONTINUED)

Abbreviation or Specialist Term	Explanation
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
IV	Intravenous
JNK	c-Jun N-terminal kinase
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein
[redacted]	[redacted]
[redacted]	[redacted]
LS	Least-squares
[redacted]	[redacted]
[redacted]	[redacted]
MCP-Mod	Multiple comparison and dose-response modeling
MED	Minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model of repeated measures

APPENDIX A: TABLE OF ABBREVIATIONS (CONTINUED)

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
[redacted]	[redacted]
NASH	Non-alcoholic Steatohepatitis
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NRI	Non-responder imputation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PE	Physical examinations
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
[redacted]	[redacted]
PO	Per os, orally
PP	Per protocol
PQC	Product Quality Complaint
[redacted]	[redacted]
PT	Prothrombin time
QD	Quaque die, once daily
[redacted]	[redacted]
QTcF	QTc calculation using Fridericia's formula
RBC	Red blood cell count
RNA	Ribonucleic acid

APPENDIX A: TABLE OF ABBREVIATIONS (CONTINUED)

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SE	Standard error
SGLT	Sodium-glucose co-transporter
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
[redacted]	[redacted]
SMT	Safety Management Team
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal Half-life
TB	Tuberculosis
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TGF- β	Transforming growth factor beta
[redacted]	[redacted]
T_{max}	Time to maximum plasma concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
[redacted]	[redacted]
VCTE	Vibration controlled transient elastography
V_z/F	Volume of distribution
WBC	White blood cell count

APPENDIX C. HEPATOTOXICITY MONITORING CRITERIA FOR INTERRUPTION AND DISCONTINUATION OF INVESTIGATIONAL PRODUCT BASED ON LIVER FUNCTION TEST ABNORMALITIES

	Laboratory Test	**Action**
Normal ALT and AST at baseline:	(ALT or AST > 3 x ULN but ≤ 8 x ULN) and (TBL< 2 x ULN and INR < 1.5)	Repeat ALT and AST within 48-72 hours. If elevations persist, evaluate other cause[a] of LTFs elevation. If the etiology is unknown, close monitoring required on a weekly basis until ALT or AST ≤ 3 x ULN or meet the criteria for discontinuation. Subjects (whether discontinued or not) are to be followed until the laboratory value returned to baseline.
	• ALT or AST > 3 x ULN and (TBL> 2 x ULN or INR > 1.5) • ALT or AST > 3 x ULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) • ALT or AST > 5 x ULN for more than 2 weeks • ALT or AST > 8 x ULN	Discontinue IP and follow-up signs or symptoms until resolution.

APPENDIX C: HEPATOTOXICITY MONITORING CRITERIA FOR INTERRUPTION AND DISCONTINUATION OF INVESTIGATIONAL PRODUCT BASED ON LIVER FUNCTION TEST ABNORMALITIES (CONTINUED)

	Laboratory Test	**Action**
Elevated ALT and/or AST at baseline:	ALT or AST > 2 x BLM or TBL > 1.5 x BLM	Repeat ALT and AST within 48-72 hours. If elevations persist, evaluate other cause[a] of AST, ALT and TBL elevation. If the etiology is unknown, close monitoring required on a weekly basis until ALT or AST ≤ 2 x BLM and TBL ≤ 1.5 x BLM or meet the criteria for discontinuation. Subjects (whether discontinued or not) are to be followed until the laboratory value returned to baseline.
	ALT or AST > 2 x BLM and (TBL > 2 x BLM or INR increased by > 0.2 from Baseline)	Discontinue IP and follow-up signs or symptoms until resolution.
	with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash, with or without eosinophilia (> 5%) during study	Temporarily interrupt or discontinue IP and follow-up signs or symptoms until resolution.
Elevated ALT and/or AST at baseline and BLM[b] < 2 x ULN	ALT or AST > 5 x BLM	Discontinue IP and follow-up signs or symptoms until resolution.
Elevated ALT and/or AST at baseline and BLM ≥ 2 x ULN but < 5 x ULN:	ALT or AST > 3 x BLM	Discontinue IP and follow-up signs or symptoms until resolution.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BLM = baseline measurement(s); IP = investigational product; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

[a] Tests for causes of increases AST or ALT include infectious (Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E), acetaminophen level, toxicology screen, autoimmune (antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal antibodies type 1, immunoglobulin G [IgG]). Additional tests and evaluations may be requested by the medical monitor. Tests of function include serum albumin and prothrombin time (PT)/INR.

[b] In subjects with screening TBL or AST or ALT, greater than 3 X ULN, baseline values should be established by at least two measurements obtained at least 4 weeks apart.

APPENDIX D. HEPATITIS EXCLUSION CRITERIA

Subjects who meet any of the Hepatitis B criteria described in the table below are ineligible for the study.

	Result	Interpretation
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection*
HBsAg anti-HBc anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities*: • Resolved infection (most common) • False-positive anti-HBc, thus susceptible • "Low level" chronic infection • Resolving acute infection

Abbreviations: HBsAg= hepatitis B surface antigen; anti- HBc= antibody to the hepatitis B core antigen; anti- HBs= antibody to hepatitis B surface antigen; IgM anti-HBC= IgM antibody to hepatitis B core antigen.
* Perform hepatitis B virus (HBV) deoxyribonucleic acid (DNA):

- If HBV DNA is **detected**, then participant must be excluded.
- If HBV DNA is **not detected**, then the participant may be considered eligible for enrollment based on the investigator's judgment and after discussion with the study Medical Monitor.

Source: Mast, 2005.

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: Friday, 16 April 2021, 12:13 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Changes included in this amendment are summarized below:

- **100 mg dose treatment arm was removed**
  - [redacted] The subjects who are randomized to the 100 mg dose group prior to implementation of Protocol Amendment 4 will stay on 100 mg QD dose throughout the study.
  - Sections affected

    Protocol Summary, Rationale (Section 1.3), Study objectives and Endpoints (Section 2), Overall Study Design (Section 3), Study Population (Section 4), Method of Treatment Assignment (Section 7.3), and Statistical Considerations (Section 9)
- **Stage 4 population was removed**
  - The protocol was revised to focus on assessing the efficacy and safety of CC-90001 in subjects with NASH and Stage 2 or Stage 3 liver fibrosis in this study.
  - Sections affected

    Protocol Summary, Rationale (Section 1.3), Study objectives and Endpoints (Section 2), Overall Study Design (Section 3), Study Population (Section 4), Table of Events (Section 5), Procedures (Section 6), Method of Treatment Assignment (Section 7.3), Statistical Considerations (Section 9), and Appendix C
- **Active Treatment/Extension Phase was removed**
  - Active treatment/extension phase was removed to reduce burden for the subjects due to the Coronavirus Disease 2019 (COVID-19) pandemic and to shorten the duration of the study. Subjects who sign informed consent form (ICF) prior to the implementation of Protocol Amendment 4 will have an option to participate active treatment/extension phase.
  - Sections affected

    Protocol Summary, Rationale (Section 1.3), Study objectives and Endpoints (Section 2), Overall Study Design (Section 3), Table of Events (Section 5), Procedures (Section 6), Method of Treatment Assignment (Section 7.3), and Statistical Considerations (Section 9)
- **Exclusion criterion #21 "Subjects has 2 positive fecal occult blood test (FOBT) during Screening, collected at least 4 weeks apart" was removed**
  - [redacted] Positive FOBT may be caused by different cuases (such as rectal hemmorhage, ulcers, colitis, divertriculosis). The protocol has excluded the subjects with a history of

inflammatory bowel disease and the subjects with a history of bleeding peptic ulcer or bleeding diverticular disease within 5 years. Furthermore, the protocol also implemented FOBT at Screening and approximately every 12 weeks during the study and discontinuation criteria for the subject with positive FOBT in the study. With all these in place the occurrence of GI bleeding in the study continues to be well monitored to ensure safety of subjects over the course of the trial.

- Sections affected

  Study Population (Section 4), Table of Events (Section 5), and Procedures – Screening Phase (Section 6.1)

- **Condition of worsening liver function was changed**
  - The values of alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) fluctuate over the short period of time as well as over the course of NASH disease. More than 20% increase of ALT or AST value in the subjects with ALT or AST less than 3 X upper limit of normal (ULN) may not be an evidence of worsening of liver function. In addition, throughout the study hepatotoxicity is monitored and subjects are to be discontinued if liver biochemistry abnormalities meet the discontinuation criteria (Appendix C). Therefore, the protocol was revised that another measurement is obtained, at least 4 weeks apart, only in the subjects with screening ALT or AST greater than 3 X ULN. If retested ALT or AST increase more than 20% the subject will be excluded from study.
  - Sections affected

    Procedures – Screening Phase (Section 6.1) and Appendix C

- **Approved weight-loss medications were removed from prohibited medications**
  - Exclusion criterion #12 was removed and inclusion criterion # 6 was revised to allow anti-obesity medications in the study if the medications have been stable for 3 months prior to Screening or historical biopsy used for Screening.
  - Sections affected

    Study Population (Section 4) and Concomitant Medications and Procedures (Section 8)

- **Changed Visit 5 Week 8 and Visit 7 Week 16 to remote visit**
  - Visit 5 Week 8 and Visit 7 Week 16 were changed to remote visit to reduce operational complexity and the burden for the subjects.
  - Sections affected

    Table of Events (Section 5) and Procedures (Section 6)

[redacted]

The amendment also includes other minor clarifications and corrections.

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this amendment is to expand the study population to allow inclusion of subjects with Non-alcoholic Steatohepatitis (NASH) and Stage 2 fibrosis. Modifications to inclusion/exclusion criteria were made to broaden the study population.

Changes included in this amendment are summarized below:

- Protocol Title (Title Page and Protocol Summary)

  The title was changed to "A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter, Dose-finding Study to Evaluate the Efficacy and Safety of CC-90001 in Subjects with Non-alcoholic Steatohepatitis (NASH) and Liver Fibrosis"

- Therapeutic Area Head signature page
  - Name and title of therapeutic area head was changed
- Protocol Summary, Rationale (Section 1.3), Study objectives and Endpoints (Section 2), Overall Study Design (Section 3), Study Population (Section 4), Method of Treatment Assignment (Section 7.3), Statistical Considerations (Section 9), [redacted] and Appendix C
  - Expanded study population to allow subjects with NASH and Stage 2 fibrosis in the study and evaluate efficacy and safety of CC-90001 in these subjects.
  - References to [redacted] Appendix C were removed from Study population, Table of Events footnote and Procedures sections because they did not apply to Stage 2 fibrosis. [redacted] Appendix C were removed as well.

[redacted]

- Study Population (Section 4) Procedures (Section 6) and Concomitant Medications and Procedures (Section 8)
  - Inclusion criterion #6 was revised to clarify that this criterion applies to all fibric acid derivatives (fibrates) and to ensure that if sodium-glucose co-transporter 2 inhibitors and glucagon peptide-1 agonists have been discontinued those medications must have been stopped 3 months prior to screening or historical biopsy. The Permitted Concomitant Medications and Procedure (Section 8.1) was updated accordingly.

- Inclusion criterion #7 was revised to change stable dose of thiazolidinediones or vitamin E from 6 months to 3 months and to ensure that if thiazolidinediones or vitamin E have been discontinued those medications must have been stopped 3 months prior to screening or historical biopsy. The Permitted Concomitant Medications and Procedure (Section 8.1) was updated accordingly.
- Exclusion criterion #4 was revised to exclude subjects with HbA1C ≥ 9.5%.

  Protocol allows for dose initiation/adjustments on of anti-diabetic medications during the study in order to optimize clinical care and safety risk to the subjects with HbA1C < 9.5% is low.
- Exclusion criterion #5 was revised to clarify that worsening of liver function is based on aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin laboratory values.
- Exclusion criterion #7 was revised to remove bariatric surgery from this criterion
- Exclusion criterion #10 was revised to remove the drugs historically associated with nonalcoholic fatty liver disease (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) from this criterion. The Prohibited Concomitant Medications and Procedure (Section 8.2) was updated accordingly.
- Exclusion criterion #17 was revised to allow subjects with a history of hepatitis C virus (HCV) and sustained viral response (undetectable HCV ribonucleic acid [RNA]) for at least 2 years prior to Screening including negative HCV RNA at Screening.
- Exclusion criterion #23 was revised to allow subjects with a history of malignancy beyond 5 years to be enrolled in the study.

[redacted]

- Exclusion criterion # 30 was revised to "Prior use of obeticholic acid or participation of obeticholic acid clinical trial within 6 months prior to Screening or historical biopsy used for Screening"
- Removed exclusion criterion #31
- Added new exclusion criterion #31 to exclude subjects with history of bariatric surgery within 5 years prior to Screening or likely to have bariatric surgery during the study
- Renumbered exclusion criteria #32 and #33 to align with the electronic case report form and updated criteria of serum total bilirubin.

- Protocol Summary, Rationale (Section 1.3), Study objectives and Endpoints (Section 2), Study Population (Section 4), Table of Events (Section 5) and Procedures (Section 6)

[redacted]

[redacted]

  - Revised exclusion criterion #13 to clarify that subjects with SARS-CoV-2 infection within 4 weeks of Screening will be excluded and symptoms must have completely resolved
  - Added exclusion criterion #34 to exclude subjects who have received live attenuated or investigational SARS-CoV-2 vaccine within 3 months prior to the first dose of study treatment.

- Clinical Laboratory Assessments (Section 6.5.3)
  - Changes were made to clarify that fasting is required for certain visits.
- Dose Interruptions (Section 7.2.2)
  - Revised to clarify that Investigational Product (IP) should be interrupted 7-10 days prior to an elective surgical procedure
- Concomitant Medications and Procedures (Section 8)
  - Use of cannabinoid products other than cannabis oils during the study was added to prohibited medication
  - Clarification and corrections were made to Permitted and Prohibited Concomitant Medications and Procedures
- Adverse Event (Section 10)
  - Clarification was made that only Serious Adverse Events occurring after first dose of IP will be reported to Celgene Drug Safety

[redacted]

- Appendix C: Hepatotoxicity Monitoring Criteria for Interruption and Discontinuation of Investigational Product Based on Liver Function Test Abnormalities
  - Clarifications were made in Appendix C
- Appendix D: Hepatitis Exclusion Criteria

[redacted]

The amendment also includes other minor clarifications and corrections.

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this amendment is to add screening α-fetoprotein test to Table of Events and Procedure sections for subjects with Stage 3 fibrosis and to clarify some of inclusion/exclusion criteria.

Changes included in this amendment are summarized below:

- Medical Monitor / Emergency Contact Information
  - Contact information was changed to replace medical monitor's phone numbers with hotline number
- Protocol Summary and Overall Study Design (Section 3)
  - Screening period was extended to 10 weeks to allow enough time for completion of study procedures.
- Study Population (Section 4)
  - Inclusion criterion #5 was updated to clarify that the historical liver biopsy in subjects who had been on therapy for treatment of NASH is not to be accepted.
  - Inclusion criteria #6 and #7 were updated to ensure stable doses of medications prior to and after historical liver biopsy is obtained, if the historical biopsy was going to be used for the inclusion criteria.
  - Exclusion criterion #3 was corrected.
  - Exclusion criterion #17 were updated to clarify that positive screening hepatitis B/C is also exclusionary for the study.
  - Exclusion criterion #31 was added to exclude subjects with history of Gilbert's syndrome since clinical manifestations of Gilbert's syndrome might confound the safety and efficacy assessments of CC-90001.
- Table of Events (Section 5) and Procedures (Section 6)
  - Added screening α-fetoprotein test to Table of Events and Procedures sections. Protocol Section 4.3.2 Exclusion Criteria for the Subjects with Stage 3 Fibrosis excludes subjects with a screening α-fetoprotein ≥ 200 ng/mL and α-fetoprotein > 20 ng/mL should be discussed with Sponsor to review the evaluation of Hepatocellular Cancer (HCC).
  - Added ultrasound and α-fetoprotein test at Early Termination Visit to ensure HCC surveillance to be done for early terminated subjects with Stage 4 fibrosis.
- Prohibited Concomitant Medications and Procedures (Section 8.2)
  - Acetaminophen dose was corrected.
- Individual Subject Stopping Criteria (Section 11.1.1)
  - Clarification was made on FOBT stopping criterion.

[redacted]

The amendment also includes other minor clarifications and corrections.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Medical Monitor / Emergency Contact Information
  - Contact information changed to the clinical research organization (CRO) medical monitor information (including Global Medical Monitor, Medical Monitor for Europe, and Medical Monitor for Asia-Pacific)
- Celgene therapeutic area head signature page
  - Name of therapeutic area head was changed.

[redacted]

- Exclusion Criteria for All Subjects (Section 4.3.1)
  - Revised exclusion criterion #4 to change Hemoglobin A1c ≥ 9.5% within 60 days prior to randomization to Hemoglobin A1c > 8% at screening due to recent consensus guidelines for the pharmacologic management of adults with Type 2 Diabetes Mellitus (DM).
  - Revised exclusion criterion #14, and added exclusion criterion #15 to further clarify the eligibility of history of active or latent tuberculosis (TB) or subject who had a household contact with a person with active TB.
  - Added exclusion criteria #19, #20, and #21 to exclude subjects with 2 positive fecal occult blood tests (FOBTs), subjects with a history of bleeding peptic ulcer or bleeding diverticular disease within the last 5 years, and subjects with a history inflammatory bowel disease [redacted] to exclude subjects with disorders of gastrointestinal (GI) bleeding.

[redacted]

- Exclusion Criteria for All Subjects (Section 4.3.1) and Prohibited Concomitant Medications and Procedures (Section 8.2)

[redacted]

  - Added exclusion criterion #26 and prohibited concomitant use of warfarin within 2 weeks prior to Screening and during study to align with inclusion and discontinuation criteria for subjects with liver disease and elevated international normalized ratio (INR).
  - Added exclusion criterion #30 and prohibited prior and concomitant use of obeticholic acid, which could potentially confound the evaluation of efficacy.

- Prohibited Concomitant Medications and Procedures (Section 8.2)
  - Prohibited initiation of Vitamin E after Screening which could potentially confound the evaluation of efficacy.
- Table of Events (Section 5) and Study Procedures (Section 6)
  - Added human immunodeficiency virus (HIV) test at Screening [redacted] Exclusion criterion #16 (previously exclusion criterion #15) was modified to exclude subjects with positive Screening HIV test.
  - Added FOBTs at Screening, approximately every 12 weeks during the study, Early Termination Visit and Post-treatment Observational Follow-up Visit [redacted] to monitor for GI bleeding during the study.
  - Added electrocardiograms (ECGs) at the Week 12, Week 66, and Week 84 visits [redacted].
- Sample Size and Power Considerations
  - Updated Table 5 "Probability of Each Dose to Be Considered the MED for Various Response Scenarios and Delta" to add "No MED identified" category
- Discontinuations (Section 11)
  - [redacted] added the following new individual subject stopping criteria:
    - A positive FOBT at a study visit and a decrease of hemoglobin from baseline by at least 10% at that study visit or subsequent visits.
    - A Grade 3 or higher drug-related AE by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading system.
    - Grade 4 or higher AE by CTCAE Version 5.0 grading system.
  - [redacted] added and modified criteria for review of clinical data by the DMC:
    - One subject develops a Grade 5 AE by CTCAE Version 5.0 grading system.
    - Two subjects develop drug-related Grade 4 AEs by CTCAE Version 5.0 grading system.

The amendment also includes other minor clarifications and corrections.